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Breast cancer survivals and hormone therapy: estrogen and melatonin

José Maria Soares Júnior[1*], Bruna Salani Mota[1], Gabriela Bezerra Nobrega[1], José Roberto Filassi[1], Isabel Cristina Espósito Sorpreso[1], Edmund Chada Baracat[1]

Climacteric is a period of transition between reproductive and non-reproductive periods. It is filled with fears and anxieties. Although many women go through this age phase without any symptoms or significant challenges, others suffer with intense vasomotor symptoms (hot flashes), which can cause perspiration and interfere with sleep if they occur at night[1]. Also, approximately 80% of breast cancer patients are above 50 years old, which matches with the mean age of menopause[1,2]. However, the behavior and prognosis of this malign neoplasia may be related to the estrogen status[3]. It is a concern for menopausal hormone treatment.

Estrogen hormone therapy is known for its benefits, such as alleviating vasomotor symptoms arising from the state of hypoestrogenism. However, long-term use can provide an increased risk of breast cancer, which brings fear for both physicians and women[4]. This relative risk (RR) of estrogen associated with progestin to develop breast cancer is around 1.25[5], which is a weak factor. The progestin is important to avoid endometrial proliferative lesions that may progress to cancer[6]. However, this unopposed estrogen breast cancer RR is not significant in hysterectomized women[7].

Regarding the RR of cancer, the values over 1:50 are considered relevant for any event. At this point, hormone therapy would have no relevant impact on the onset of breast cancer compared to familial or genetic risk[8]. However, the fear is still very great in the perception of women in relation to breast cancer. Non-hormonal therapy could be an alternative, but side effects and lack of improvement are the main reasons for non-adherence to patients[8]. Therefore, estrogen therapy is still more effective for this treatment.

Some breast cancer survivors experience hot flashes without improvement when treated by the non-hormonal drugs, mainly serotonin reuptake inhibitors, as well as the inhibitors of reuptake of noradrenaline and serotonin and other substances[9]. It is a great concern to alleviate these symptoms, which affect sleep patterns, professional activities, and quality of life[1,2]. The hormone therapy with estrogen is a controversial question: it decreases the symptoms, but may impact the prognosis of the patient[1-3,8]. The HABITS trial showed 2.4 times more risk of new breast cancer events in breast cancer survivors with a cumulative incidence of 22.2% in the group taking hormone replacement versus 8% in the control arm at 5 years[10].

Recently, Mendoza et al.[11] reported a new view in the use of hormone therapy in the climacteric, including classifying it into categories, which is similar to hormonal contraceptive during the reproductive period by the World Health Organization[11]. In addition, the authors suggest that hormone therapy with estrogen could be indicated in women with triple negative breast cancer[11], but the evidence supporting this conduct is few and the prognosis of this type of breast tumor is lower than that with positive receptor[11]. These findings were supported by Poggio et al.'s[12] meta-analysis of four clinical trials with 4050 patients randomized to receive estrogen/progestogen or tibolone against placebo or no hormone therapy. The hormone replacement increased the risk of breast cancer recurrence by 46%, ranging from 12 to 91% according to the confidence interval, but only in the hormone receptor positive subgroup analysis (HR 1.8, 95%CI 1.15–2.82, p=0.010). The triple negative group had no risk (HR 1.19, 95% CI 1.15–1.77, p=0.39). For these reasons, this proposal is still controversial. However, the North American Menopause Society states that if the patient has decreased quality of life and has tried other non-hormonal treatments without adequate results, hormone therapy should be discussed with the patient[13].

In general, estrogen has its proliferative effect on breast tissue due to intracellular signaling after activation of the alpha receptor on the cell membrane, whose pathway involves the

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mitogenic protein[14]. In this process, there is interaction with the activation of cyclic AMP and PKA, which are also the target of melatonin signaling[15], and this could interfere with the estrogenic mitogenic action in the breast tissue[14].

Melatonin has oncostatic actions that are exerted through different mechanisms: indirect effects by reducing ovarian estrogen production; direct anti-estrogenic actions at the level of tumor cells; induction of apoptosis; antioxidant effects; increased anti-neoplastic immunity; reduction of telomerase activity; inhibition of fatty acid uptake and metabolic pathways of fat; and inhibition of angiogenesis[16].

Regarding its anti-angiogenic effects, melatonin reduces the expression of vascular-endothelial growth factor (VEGF) mRNA in MCF-7 cells and inhibits proliferation, invasion, and migration of endothelial cells and formation of tubular networks induced by VEGF[16-18]. Similarly, melatonin indirectly inhibits angiogenesis through the repression of IGF, EGF, and ET-1 (tumor growth factors and tumor angiogenesis enhancers) and decreases the production of ROS, which has an important function in the stabilization of the hypoxia-inducing factor-α during hypoxia[16].

In patients with estrogen receptor (ER) positive breast cancer, melatonin appears to have an inhibitory action on estrogen-mediated cells. It presents an anti-cancer effect because of two membrane protein named MT1 receptor and MT2 receptor. The oncostatic effect in breast cancer is achieved by the suppression and inhibition of ER mRNA. Besides that, melatonin also regulates the metabolism of other steroid hormone and nuclear receptor family members, which interferes with the effect of the estrogen on breast tissue[19].

Melatonin acts on the sleep of postmenopausal women with breast cancer, but without improvement in vasomotor symptoms[20]. Furthermore, it seems to have a synergic effect with other anti-neoplastic treatments, with the reduction of toxicity[19]. Perhaps, a combination of estrogen and melatonin could be beneficial for women with intense vasomotor symptoms. However, there is a need for studies, and perhaps this is the great challenge of the future: optimal hormone replacement in women who have had breast cancer.

AUTHORS' CONTRIBUTIONS

JMSJ: Conceptualization, Writing – original draft, Writing – review & editing. **BSM:** Conceptualization, Writing – original draft, Writing – review & editing. **GBN:** Writing – original draft. **JRF:** Writing – review & editing. **ICES:** Writing – review & editing. **ECB:** Conceptualization, Writing – original draft, Writing – review & editing.

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Importance of human papillomavirus genotyping and standardized sampling in men

Mehmet Sarier[1,2*]

At present, the most common sexually transmitted disease in the world is caused by human papillomavirus (HPV) and is associated with a significant global socioeconomic burden[1]. Vaccination is the most important step in the management of HPV. However, despite the progress in vaccination studies in recent years, the disease cannot be said to be under control. An important reason for its widespread is that the vast majority of cases are asymptomatic, and, in particular, sexually active individuals continue to be contagious like vectors. Nucleic acid amplification tests (NAATs) such as PCR (polymerase chain reaction) are the diagnostic gold standard because serological tests are inadequate in the diagnosis of HPV[2]. Due to the strong association between HPV and cervical and other anogenital carcinomas, the vaginal swab sample has been used successfully for HPV genotyping in women for many years. However, men are the other side of the HPV management coin, and there lies a serious problem. As is known, the U.S. Food and Drug Administration (FDA) does not recommend HPV tests for men[3]. This means that the presence of HPV in men can be ascertained by clinicians only in the presence of genital warts or symptomatic infection. However, genital warts usually manifest with low-risk HPV types. As a result, most HPV-positive men, especially those with high-risk HPV types, remain undiagnosed. The relationship between HPV and penile cancer has long been known, and recent studies have also provided evidence of a strong association between HPV and urothelial carcinoma of the bladder[4]. We believe that the FDA's position on this matter requires reconsideration.

There is also a gap regarding the effective sampling method for HPV genotyping in men. Of course, the FDA's decision has a large influence on this. This decision may also be related to the limited number of published reports on this subject. Standardization is needed for accurate and effective sampling in men. In asymptomatic patients, the inside of the foreskin is a recommended swab sampling site, while anal swab/cyto-brush samples are widely used in men who have sex with men (MSM)[5,6]. However, the approach for circumcised and heterosexual men is unclear. In our opinion, a standard should be established for sampling all men—MSM or heterosexual, circumcised or uncircumcised—with the same diagnostic efficacy. According to previous publications, there is no common approach among sampling methods for HPV genotyping in men due to the above differences. In addition, as PCR technology continues to develop and HPV typing is performed more routinely, it is has become clear that HPV types other than the most well-known HPVs (6, 11, 16, and 18) are more common than expected, and that people often carry multiple HPV types[7]. This shows that HPV management in men needs an update. In a recent study, PCR analysis of swab samples from multiple sites and the wart itself in male patients presenting with genital warts, 78.2% of these patients had multiple HPV types and 71.9% had at least one high-risk HPV type[8]. We think that the importance of male factor in the control of HPV infection will become more evident in future. Therefore, researchers need to work more intensively to establish standard sampling protocols with high diagnostic efficacy for HPV-DNA screening tests. For this to happen, we hope that the FDA will reconsider its position on HPV genotyping tests in men.

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Inflammatory markers as outcome predictors of COVID-19 in pregnant women

Ana Claudia Fiorini[1,2], Antonio Carlos Guimaraes de Almeida[3], Fulvio Alexandre Scorza[4], Josef Finsterer[5*]

Dear Editor,

We read with interest the article by Gündüz et al. on a cross-sectional study of 464 pregnant women with asymptomatic/mild (group 1) or severe (respiratory rate >24 and saturation <93%) SARS-CoV-2 infection (group 2) regarding the prognostic value of blood inflammatory markers for the outcome of COVID-19[1]. The neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and the systemic inflammatory index (SII) were found to predict the outcome of COVID-19[1]. The study is excellent but has limitations that should be discussed.

The number of patients within each group differs markedly between the two groups. For this reason, a statistical comparison is problematic and not reliable.

The severity of SARS-CoV-2 infection was assessed only by the presence or absence of dyspnea. However, SARS-CoV-2 infections often manifest in extra-pulmonary organs[2]. Therefore, we should know the number of patients in whom the SARS-CoV-2 infection first manifested itself in organs other than the lungs.

Since D-dimer is increased per se due to the pro-thrombotic state in pregnancy, especially in the first and third trimester[3], it should not be used as an inflammatory parameter of COVID-19. The elevated D-dimer levels can lead to false positive results.

Patients with severe COVID-19 are susceptible to secondary infections due to immunosuppression by the SARS-CoV-2 virus[4]. Therefore, the number of pregnant women in whom the increase in inflammatory parameters was due to superinfection and not due to the COVID-19 infection should be clarified.

The prognosis of SARS-CoV-2 infection in pregnant women should not only be based on serum inflammatory markers, but also on monocyte distribution range, blood gas analysis, and imaging methods such as X-ray or CT of the lungs[5]. Antibody titres and CD3, CD4, and CD8 cell counts are even more specific than the inflammatory parameters evaluated for the study.

Another limitation is that the current medications taken regularly by the included women were not reported. Knowledge of current medications is critical, as multiple drugs can affect the blood parameters evaluated for the index study. For example, how many of the included patients had epilepsy and were taking anti-seizure drugs? The comorbidities are also absent. Knowledge of comorbidities is of crucial importance due to their impacts on the evaluated parameters.

There is no mention of the correlation between the inflammatory parameters and the outcome of the pregnancy. How many of the included patients had a stillbirth, an abortion, bleeding, premature rupture of membranes, placenta previa, or a cesarean section?

How many of the included patients had an elevated D-dimer level? Have these patients been screened for thrombosis? Another limitation of the study is that smoking status of pregnant women was not reported.

What was the cause of death of the two deceased patients? Did they die from COVID-19 or other causes? Have they been autopsied?

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these limitations would strengthen the conclusion and could improve the study. Inflammatory markers should not be the only predictors of COVID-19 in SARS-CoV-2-infected pregnant women.

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DATA ACCESS STATEMENT

All data are available from the corresponding author.

ETHICAL COMPLIANCE STATEMENT

The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

JF: Conceptualization, Formal Analysis, Validation, Visualization, Writing – review & editing. **ACF:** Supervision, Validation. **FAS:** Supervision, Validation.

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Socio-economic factors are the main factors affecting organ donation

Meng Li[1], Han Li[2], Ali Sorayyaei Azar[3]*

Dear Editor,

We were delighted to come across the high-quality research article by Martino et al.[1] entitled "Attitude and knowledge of medical students toward donation after circulatory death." The study aimed to investigate and analyze the acceptance of organ donation in Brazil. Martino et al. conducted a survey among medical students at a public university in Brazil, utilizing a questionnaire comprising 26 goals and Likert scale questions. The results revealed that a majority of participants were familiar with the concept of brain death, and the acceptance of postmortem donation was significantly higher than that of living donation. These intriguing findings and valuable results have captured our interest. However, upon further reading and investigation, we believe that the conclusions reached by Martino et al. warrant additional exploration and research. We are enthusiastic about contributing to the ongoing debate and eagerly anticipate hearing from the authors.

First and foremost, it is important to note that the authors of the study did not conduct a multi-center survey. The sample solely consisted of medical students from a public university in Brazil. By drawing conclusions based on a single center, the study deviated from the principles of a multi-center approach. It is well established that relying on a single sample source can significantly diminish the reliability of conclusions. There are various potential confounding factors that can influence medical students' perceptions of organ donation, both living and postmortem. These factors may include the geographic environment, household income, cultural influences, regional policies, etc. Moreover, these factors can often interplay with one another. Additionally, differences in educational levels among various universities can contribute to distinct cognitive perspectives among students. Students attending higher-level universities may display a higher acceptance of organ donation, whereas those attending lower-level universities may exhibit relatively lower acceptance rates[2]. Therefore, it is strongly recommended that the authors supplement their study with multi-center surveys to enhance the reliability of the data.

Furthermore, we observed that the authors compared the willingness of Chinese students to donate kidneys to their relatives while alive with that of Brazilian medical students. However, it is important to acknowledge that the comparability between these two groups is relatively low due to the profound influence of Confucianism and culture in China. Chinese students are often influenced by family ethics and humanistic values, which may contribute to their increased willingness to donate organs to their relatives. Additionally, the authors mentioned the proportion of liver donation. It is worth noting that the liver has the remarkable ability to regenerate fully with just 30% of its original mass. As individuals with medical education are likely to be aware of this fact, they may exhibit greater acceptance of liver donations, whether in vivo or posthumously.

Finally, it is worth noting that the author highlights a distinction between Eastern and Western countries regarding organ donations. According to the authors, Eastern countries, particularly China and Japan, heavily influenced by Confucianism, face difficulties in accepting living donations compared to postmortem donations. This is due to the emphasis on filial piety in Confucian culture, where the preservation of one's body, including hair and skin given by parents, is considered paramount: "My body, including hair and skin, which is given by parents, shouldn't be damaged. This is the basic principle of filial piety." Filial piety holds great significance in these countries[3]. On the contrary, some scholars[4,5] argue that socioeconomic factors, rather than religious beliefs or other considerations, are the primary barriers to organ donation in Western countries.

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All other authors have read the manuscript and have agreed to submit it in its current form for consideration for publication in the Revista da Associacao Medica Brasileira.

AUTHORS' CONTRIBUTIONS

ML: Conceptualization, Formal Analysis, Writing – original draft. **HL:** Conceptualization, Formal Analysis, Writing – original draft. **ASA:** Writing – review & editing.

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ORIGINAL ARTICLE

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Peak nasal inspiratory flow in children and adolescents with sickle cell disease: a case-control study

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SUMMARY

OBJECTIVE: Sickle cell disease is the most frequent of the hereditary hemoglobinopathies and it presents multisystemic effects. A manifestation that is commonly found in sickle cell disease is upper airway obstruction, particularly adenotonsillar hypertrophy. This study aims to evaluate the peak nasal inspiratory flow measurements of children and adolescents with sickle cell disease.

METHODS: This is a case-control study on children aged between 8 and 15 years who were diagnosed with sickle cell disease. Peak nasal inspiratory flow measurements were obtained from patients.

RESULTS: A total of 279 patients were enrolled in this study, with 93 in the case group and 186 in the control group. The case group had an 82.83% chance of having lower peak nasal inspiratory flow values than the control group. In the case group, 75% of the peak nasal inspiratory flow values were in the lower standards, whereas in the control group, only 25% were in the lower standards.

CONCLUSION: This study showed a high prevalence of reduced peak nasal inspiratory flow values in children with sickle cell disease and could certainly be incorporated into the day-to-day clinical evaluation of patients as a screening instrument.

KEYWORDS: Sickle cell disease. Hemoglobinopathies. Rhinomanometry. Acoustic rhinometry. Hypoxemia.

INTRODUCTION

Sickle cell disease (SCD) is the most frequent of the hereditary hemoglobinopathies. Its most important pathophysiological aspect is in the red blood cell sickling phenomena with multisystemic effects[1]. Among these effects are manifestations in the upper airways. Furthermore, SCD is a group that is too often neglected in research worldwide. Incidence in Brazil is variable depending on the region, occurring at a rate of approximately 1:1400 to 1:1650 live births in the most prevalent regions[2]. Similar data were found in England at a rate of 1:2000[3]. This represents a high incidence when compared to other countries such as the United States of America, with a rate of 1:6600, according to neonatal screening in the state of California[3].

The infected children and adolescents often suffer from upper airways respiratory diseases. Adenotonsillar hypertrophy (AH) is most commonly found in patients with SCD[4]. It is speculated that this occurs as a result of repeated infections of the upper airways, secondary to functional asplenia[5]. AH is an important causal factor in obstructive sleep apnea syndrome and hypopnea in children[6]. Respiratory sleep disorders are often related to the drop-in oxygen saturation (SaO_2) during the night. Nocturnal desaturation in patients with SCD is associated with high rates of vaso-occlusive pain crises in children, as well as an increase in the probability of events related to the central nervous system (CNS)[7]. Among these CNS events, it is worth highlighting silent infarcts, which produces high morbidity, and leads to significant neurocognitive deficits[7].

Despite the importance of the symptoms related to the upper airways, there are no existing studies in the literature describing objective assessment for nasal air flow in SCD. The peak nasal inspiratory flow (PNIF) is a simple, low cost, and easy-to-use method[8]. Besides this, it presents a reference curve for a pediatric age bracket, which greatly facilitates its use in clinical practice. The assessment of PNIF is useful, informative, and reproducible, particularly when compared to expensive methods such as rhinomanometry and acoustic rhinometry[9]. Since previous studies demonstrated good correlation between rhinomanometry results when compared to PNIF measurements, we decided to use this valuable tool[8,9]. Furthermore, there is a paucity of information in the literature on diagnosing upper airway obstruction in patients with

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SCD, especially in the pediatric population. Therefore, this study is justified to assist the physicians in clinical practice.

The aim of this study was to perform a case-control study evaluation of the PNIF measurements for children and adolescents with SCD ranging in age from 8 to 15 years and to verify the association of the values obtained with variables of interest, such as hematological indices, oxygen saturimetry, past tonsillectomy, and/or adenoidectomy.

METHODS

The case-control study was carried out at the *Fundação Centro de Hematologia e Hemoterapia de Minas Gerais* (Minas Gerais Hematology and Hemotherapy Foundation Center - HEMOMINAS) and at public schools, in the city of Belo Horizonte, Minas Gerais State, Brazil. The case group was composed of children and adolescents with SCD, ranging in age from 8 to 15 years. The control group was composed of children and adolescents without SCD or any upper airway disease ranging in age from 8 to 15 years.

Inclusion and exclusion criteria

Children and adolescents selected by PETN-MG were included in the study composing the case group. All patients had been diagnosed and confirmed at the age of 1 year. The SS and $S\beta^0$ thalassemia genotypes were included, with ages ranging from 8 to 15 years. Children and adolescents from various public and private schools in Belo Horizonte, Minas Gerais State, without SCD were included in the study, composing the control group. All patients from both the groups who presented acute infection of the airways or were unable to perform the respiratory maneuvers were excluded from the study.

Procedures

Data on the case group were collected through interviews, physical assessment, and research of medical records. The interview was performed using a semi-structured questionnaire. Physical assessment was based on the gathering of vital data, including the measurement of weight and height. Research of medical records consisted in retrieving relevant data such as surgery on tonsils and adenoids, chronic transfusion, and hydroxyurea use.

Data on the control group were collected through physical assessment, questionnaire of upper airway symptoms, and PNIF measures (*In-check-inspiratory flow meter*, Clement Clarke, Harlow, England). Before PNIF measurements, the patient performed routine nasal hygiene by gently blowing the nose to eliminate residual nasal secretion. The facial mask was duly placed with participants standing up. They were then told to take a vigorous nasal inspiration from the residual capacity. At least three measurements were taken, and the highest value obtained was considered for analysis. The value noted was compared between the case and control groups.

Statistical analysis

Patient selection was done by non-probability sampling. Descriptive analysis was used to characterize population. With the goal of comparing the results of the two groups of children (case and control – the last one being the compound of two control groups) to the measure of PNIF, withdrawing the effect of the existing differences between each of the groups (blocks), that is, considering the dependence among the three groups of children (case, control 1, and control 2) once they were matched by age and sex, a variance analysis based on block planning with one factor (three groups of children) was performed. The use of block planning aims to withdraw the effect of variation caused by the difference between the experimental units (in this study, the children). The goal of the analysis in this study is to compare the obtained mean values of PNIF by each of the groups (case and control), i.e., to evaluate whether the PNIF measures in both groups presents different mean values or not in a set of paired children. The variance analysis based on block planning with one factor may be understood as an extension of the Student's t-test for paired samples, however, to compare the measures of PNIF performed in three paired groups. The p-value considered statistically significant was lower than 0.05. Univariate analysis was employed to evaluate the correlation between the variables studied through PNIF, tonsillectomy, and oxygen saturimetry. Comparison of the three saturimetry ranges (SaO_2 >98, 95–98, and <98%) was done based on analysis of variance.

Ethical aspects

The protocol and Informed Consent Form were approved by the Research Ethics Committee of HEMOMINAS and the Federal University of Minas Gerais.

RESULTS

The PNIF measurements of 279 individuals were analyzed, of whom 93 were in the case group and 186 were in the control group, comprising control groups 1 and 2. There was no statistically significant difference between the groups of boys and girls in terms of age, weight, height, and PNIF percentage in relation to the expected value (PNIF%). Table 1 shows the descriptive characteristics of the population studied.

The comparison between the PNIF values in the control and case groups by variance analysis showed a probability of

82.83% that the SCD child has a lower PNIF value than the control child, as shown in Table 2.

The mean value of PNIF in the SCD group was 88.5±26.2, and in the control group it was 109.7±16.9, as shown in Table 3.

DISCUSSION

This study found that the majority of the SCD children and adolescents group (75%) presented values of PNIF at the same level as the minority (25%) of the healthy control group, indicating that lower values of PNIF are more prevalent in this population than in the general one. The 82.83% probability of the PNIF values to be lower in the case group than in the control group reinforces that understanding.

This study is pioneer in its analysis of an objective method for measuring nasal inspiratory flow in individuals with SCD and has begun to fill the gap in the literature while serving as base for new studies. Additionally, the originality and lack of studies with similar methodology make it more complex to compare the data from this study with others. The association between SCD and some upper airway respiratory diseases has been demonstrated in publications, especially tonsillar hypertrophy and turbinate hypertrophy[10-15]. Considering that these afflictions have the potential to affect nasal air flow, and PNIF being a method for measuring this flow, it could become an important tool in the evaluation of patients with SCD. The irrefutably altered values noted in this experiment corroborate this possibility. Therefore, this study presents a practical possibility of incorporating a low-cost and easy-to-use device in the physician's clinical practice.

It is important to note that a limitation of the study is that it does not manage to demonstrate the factors that influence PNIF values in patients with SCD. Another significant limitation is that this study was conducted in only one reference center in Minas Gerais; therefore, caution is suggested to generalize outcomes. New studies must be carried out in other reference centers using different methodologies and clinical laboratory parameters.

Table 1. Children participating in the study, distributed by group, age, and sex.

Age (years)	Groups					
	Case		Control 1		Control 2	
	Male	Female	Male	Female	Male	Female
8	5	8	5	8	5	8
9	6	7	6	7	6	7
10	7	7	7	7	7	7
11	4	2	4	2	4	2
12	4	6	4	6	4	6
13	4	7	4	7	4	7
14	7	11	7	11	7	11
15	2	6	2	6	2	6
Total	39	54	39	54	39	54

Table 2. Variance analysis based on a block model comparing the two groups of children regarding the peak nasal inspiratory flow values.

Variation source	Sum of squares	D.F.	Mean squares	F	p
Group	27947.314	1	27,947.314	82.827	**<0.001**
Block	53762.244	92	584.372		
Error	62,422.020	185	337.416		

F: variance analysis statistics based on a block model (93 children), p: test significance probability, D.F.: degrees of freedom. Bold indicates statistically significant value.

Table 3. Descriptive and comparative measures of peak nasal inspiratory flow in both groups of children.

Group	Descriptive measures				p
	Minimum	Maximum	Mean	SD	
Case	40.0	160.0	88.5	26.2	**<0.001**
Control	80.0	160.0	109.7	16.9	

SD: standard deviation. Bold indicates statistically significant value.

Current clinical monitoring of this hematological disease has not yet incorporated objective parameters into the evaluation of nasal flow and is focused more on costly image analysis to clinically evaluate the airways. The use of a functional parameter to evaluate the upper airways could enrich the monitoring process, facilitate treatment decisions and prevent systemic complications. However, to be certain of the effectiveness of PNIF measurements, more studies are needed to address other aspects of the disease's repercussions, relating them to nasal air flow, as well as a comparison with other objective methods for nasal patency evaluation, such as rhinomanometry and acoustic rhinometry.

This study showed the existence of a high prevalence of low PNIF values in individuals with SCD. In this context, more research is needed to determine the cause of this compromised nasal airflow among these patients, as well as the factors associated with reduced PNIF. In the future, it would be interesting to verify the impact of an improvement in the levels of this parameter in the systemic course of the disease. On the contrary, although it may be a preliminary and pioneering study, results provide fundamental information. Hence, in future research, PNIF is incorporated into the methods for the evaluation and follow-up of patients with SCD.

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AUTHORS' CONTRIBUTIONS

AKV: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **CGA:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing. **CCI:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. R**RD:** Conceptualization, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing. **RMOR:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **MVDB:** Conceptualization, Data curation, Software, Writing – review & editing. **CPB:** Conceptualization, Writing – review & editing.

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ORIGINAL ARTICLE

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The new prognostic factor in pre-intubation follow-up of critically ill patients: integrated pulmonary index monitoring

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SUMMARY

OBJECTIVE: The objective of this study was to identify the integrated pulmonary index in the follow-up of non-intubated critically ill patients in the emergency department and its efficacy in deciding on advanced airway application in comparison with the Glasgow Coma Scale.

METHODS: This is a prospective, single-center, methodological study. In our study, we recorded the demographic characteristics, Glasgow Coma Scale, and the integrated pulmonary index of 90 patients with respiratory failure who were followed up in the emergency department between June 1, 2019 and September 1, 2019, and we compared the results of Glasgow Coma Scale and integrated pulmonary index in making the endotracheal intubation decision.

RESULTS: Endotracheal intubation was applied to 30% of the 90 patients included in the study. The area under the curve was calculated as 0.906 for integrated pulmonary index and 0.860 for Glasgow Coma Scale in predicting endotracheal intubation. There was no significant difference between the area under the curves of integrated pulmonary index and Glasgow Coma Scale. According to the best cutoff values determined in the estimation of endotracheal intubation, sensitivity was 74.07% and specificity was 95.24% for integrated pulmonary index, and sensitivity was 74.07% and specificity was 85.71% for Glasgow Coma Scale.

CONCLUSION: The integrated pulmonary index monitoring provides an objective evaluation in the follow-up of critically ill patients with spontaneous breathing in the emergency department and is predictive in deciding on timely endotracheal intubation.

KEYWORDS: Intensive care unit. Glasgow Coma Scale. Critical care.

INTRODUCTION

The critically ill patients are a group of physiologically unstable patients, whose clinics should be followed closely and whose treatment should be given attention and speedily[1]. In emergency departments (ED) and intensive care units (ICU), the Glasgow Coma Scale (GCS) is a universal scoring system and is used as a basic part of critically ill patients' follow-up in evaluating the neurological status of patients and deciding on advanced airway application[2]. GCS is a scoring system used for the assessment of impaired consciousness in all types of critically ill and trauma patients. The scale evaluates patients according to eye-opening, verbal, and motor responses, and reports each one separately, giving a result between 3 and 15[3]. GCS gives a general idea when stated verbally; however, some studies show that GCS presents differences between registrants among the inadequacies of scoring in prognosis follow-up, and it is stated that it causes delays in the decision of the physician to apply the neurological status and advanced airway[4-6]. It has also been shown in studies that GCS predicts mortality well in the extremes but poorly in the moderate range, and therefore its prediction capacity is anchored by the endpoints. It has been stated that there is a need for easier, understandable scoring in critical patient's follow-up[7].

In critically ill patient's follow-up in the ED and ICUs, oxygen saturation (SpO_2), respiratory rate (RR), heart rate (HR), blood pressure, central venous pressure, mixed venous oxygen saturation, and lactate are the most important follow-up parameters[8]. Many scoring systems have been developed for the neurological follow-up of critically ill patients and in deciding on advanced airway application. In addition to these scorings, the use of devices containing objective data will help physicians to follow up critically ill patients quickly and effectively. In the studies conducted on high-risk patients' follow-up in the ICU, it was emphasized that integrated pulmonary index (IPI) could predict respiratory failure in high-risk patients and could be objective and useful for respiratory monitoring in the ICU[9].

The IPI algorithm is a real-time continuous measurement of the patient's respiratory status that uses the end-tidal carbon dioxide ($PetCO_2$), HR, RR, and SpO_2 parameters to evaluate the patient's ventilation and oxygenation,

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and combines them in a mathematical model to obtain an index value. It is a non-invasive scoring system in which it is reduced to a single value where it is represented[10,11]. In our study, we investigated the effectiveness of the IPI in the follow-up of non-intubated critically ill patients in the ED and its efficacy in deciding on advanced airway application in comparison with the GCS.

METHODS

Study design and setting

This is a single-center, prospective, methodological study. The medical records of 90 patients who were admitted to the Emergency Medicine Department of Kanuni Sultan Süleyman Training and Research Hospital between June 1, 2019 and September 1, 2019, with a diagnosis of respiratory failure and planned for invasive mechanical ventilation support were examined. We informed all patients about the study and its procedures and collected informed consent on paper from the patients before their inclusion in the study. The common feature of all patients was that they were followed up in the emergency intensive care unit (EICU) with respiratory failure and invasive mechanical ventilation support was planned because there was no effective response after appropriate medical treatment and non-invasive mechanical ventilation treatment, and if the indication occurred, the patients were intubated in the EICU. A total of 5689 patients, who were followed up with red area triage coding in the ED with major and minor trauma, cases with emergency surgical intervention indication, and patients who were referred to an external center were excluded from the study, whereas 90 patients who were treated and followed up with respiratory failure in the EICU were included in the study.

Patients

We reviewed the demographic characteristics and the IPI algorithm of 90 patients followed up with respiratory failure in the EICU and evaluated its efficacy in predicting 30-day mortality and making the decision for endotracheal intubation (ETI) in comparison with GCS.

Test methods

The IPI algorithm is a non-invasive algorithm that uses the patient's respiratory status and displays it as a single index value from 1 to 10, where 8–10 indicates nearly normal ventilation, a level of ≤6 indicates that intervention may be necessary, and a level of ≤4 indicates that intervention is ultimately necessary[11].

When we look at the literature, we see that the IPI is mostly used to evaluate the weaning process and to confirm pulmonary embolism in patients admitted to the ED with respiratory failure[9,10,12]. We recorded the value at the 10th minute of the measurement of the IPI of the critically ill patients whom we examined and treated in the EICU using the Capnostream-20 monitor. We compared the scoring results with admission GCS and laboratory parameters. The ethical approval was obtained from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital *(KAEK/2019.05.130)*. It was conducted in compliance with the principles of the Declaration of Helsinki. The results of this study were reported according to the recommendations of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[13].

Statistical analysis

Descriptive analyses were presented using median [Interquartile range (IQR)] for non-normally distributed data or n (%) for categorical variables. The Shapiro–Wilk test was used to test the normality of the data. The receiver operating characteristic (ROC) curve analysis was applied to determine the optimal cutoff point of IPI and GCS for predicting the ETI, ICU stays, and 30-day mortality. The area under the curve (AUC), sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), and accuracy were calculated and reported with 95% confidence intervals. Delong et al.'s method was used for the comparison of AUCs [ref]. The optimal cutoff point of measurements was determined as the value of the maximum Youden index. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). A two-sided p-value <0.05 was considered statistically significant[14].

RESULTS

A total of 90 patients were included in the study. The median age of the patients (n=90) included in the study was 71 years (IQR: 62–80). Of note, 52.2% of the patients were males. The number of patients who had the habit of smoking was 22 (24.4%). The comorbid diseases and the laboratory values of the patients are shown in Table 1. ETI was applied to 30% of the patients followed in the EICU, whereas 44.4% were treated in the ICU, 34.4% were in the service, 20% were discharged, and 1 patient died. The patients had a 30-day mortality rate of 25.6% and a median mortality time of 2.5 days.

The AUC was calculated as 0.906 (95%CI: 0.826–0.957) for IPI and 0.860 (95%CI: 0.771–0.924) for GCS in predicting ETI. There was no significant difference between the AUC

Table 1. Demographic characteristics and the final diagnosis of the patients.

Variables (n=90)	
Age, median (IQR)	71 (62–80)
Gender, n (%)	
Female	43 (47.8)
Male	47 (52.2)
Smoking, n (%)	22 (24.4)
HT, n (%)	37 (41.1)
CAD, n (%)	17 (18.9)
DM, n (%)	9 (10)
Arrival examination, median (IQR)	
pH	7.32 (7.28–7.4)
Lactate	2.24 (1.58–3.41)
PCO_2	47.35 (39.9–57.2)
HGB	12.25 (10.5–14.1)
PLT	238 (161–315)
WBC	9.99 (8.42–14.09)
Urea	45.5 (33–68)
Creatinine	1 (0.75–1.46)
Sodium	138 (135–140)
Potassium	4.5 (4.1–5.2)
CRP	39.08 (2.82–98.23)
IPI, median (IQR)	7 (4-8)
GCS, median (IQR)	13 (10–15)
Endotracheal intubation	27 (30)
Hospital discharge	
ICU	40 (44.4)
Service	31 (34.4)
Discharge	18 (20)
Exitus	1 (1.1)
30-day mortality, n (%)	23 (25.6)
Mortality, n (%)	39 (43.3)
Mortality day, median (IQR)	2.5 (1–35)

CAD: coronary artery disease; CRP: C-reactive protein; DM: diabetes mellitus; GCS: Glasgow Coma Scale; HGB: hemoglobin; HT: hypertension; ICU: intensive care ünit; IQR: interquartile range; IPI: integrated pulmonary index; PLT: platelet; WBC: white blood cell count.

values of IPI and GCS (p=0.413). For IPI and GCS, the best cutoff values determined by the Youden index in estimating intubation were ≤4 and ≤12 (Table 2). According to the best cutoff values determined, sensitivity was 74.07% and specificity was 95.24% for IPI, and sensitivity was 74.07% and specificity was 85.71% for GCS. Accuracy was 88.9% (+LR: 15.56 and -LR: 0.27) for IPI and 82.2% (+LR: 5.19 and -LR: 0.3) for GCS (Table 3).

For the 30-day mortality estimate, the AUC for IPI was 0.794 (95%CI: 0.696–0.872) and 0.851 (95%CI: 0.761–0.918) for GCS. The difference between the AUC values of IPI and GCS was not significant (p=0.282). For IPI and GCS, the best cutoff values determined by the Youden index in predicting 30-day mortality were ≤4 and ≤12 (Table 3). According to the best cutoff values determined, sensitivity was 60.87% and specificity was 86.57% for IPI, and sensitivity was 73.91% and specificity was 82.09% for GCS. Accuracy was 80% (+LR: 4.53 and -LR: 0.45) for IPI and 80% (+LR: 4.13 and -LR: 0.32) for GCS (Table 3).

DISCUSSION

This study aims to evaluate IPI monitoring in comparison with GCS in making ETI decisions in critically ill patients' follow-up in the EICU. In the 4th National Audit Project of the Royal College of Anaesthetists and Difficult Airway Society (NAP4) study in England, due to complications that may develop during emergency airway provision, it has been reported that 31% of ED patients and 60% of ICU patients have permanent neurological damage or death. Based on the cases reported to NAP4 from ED and ICUs, it was reported that the airway could not be evaluated frequently, and more importantly, it was stated that the high-risk patient could not be identified and followed up with an appropriate airway strategy[15]. A complete airway assessment in critically ill patients has often been reported to be impractical[16]. Loss of situational awareness was determined as the most common cause of problems in 40% of the cases reported to NAP4 and it is recommended that critically ill patients be monitored and evaluated with SpO_2, $PetCO_2$, electrocardiography, and non-invasive blood pressure[17].

IPI monitoring can improve clinicians' ability to recognize patients with respiratory distress earlier, by collecting four variables in a single parameter and tracking trends in a single variable instead of four separate variables. Recognition of this downward trend in IPI may allow early recognition of clinical deterioration and timely intervention in patients and may prevent time-wasting in making intubation decisions.

Yasutoshi et al. reported that the evaluation of the IPI monitoring might be useful for respiratory monitoring in post-anesthesia care units (PACUs) and ICUs after general anesthesia. Therefore the IPI can predict the occurrence of respiratory compromise in high-risk patients in PACUs[9]. Ramandeep et al., in their study on the association of low IPI values with extubation failure, observed that decreasing IPI measurements over

Table 2. Comparison of area under the curves of the receiver operating characteristic curves of integrated pulmonary index and Glasgow Coma Scale data.

	IPI	GCS	p
Endotracheal intubation			
AUC (95%CI)	0.906 (0.826–0.957)	0.860 (0.771–0.924)	0.413
Youden index	0.693	0.598	
Associated cutoff	≤4	≤12	
ICU stay			
AUC (95%CI)	0.808 (0.711–0.883)	0.789 (0.690–0.868)	0.724
Youden index	0.480	0.465	
Associated cutoff	≤7	≤14	
30-day mortality			
AUC (95%CI)	0.794 (0.696–0.872)	0.851 (0.761–0.918)	0.282
Youden index	0.474	0.560	
Associated cutoff	≤4	≤12	

AUC: area under the curve; GCS: Glasgow Coma Scale; IPI: integrated pulmonary index.

Table 3. Cross-tabulation of integrated pulmonary index and Glasgow Coma Scale results by the occurrence of endotracheal intubation, emergency intensive care unit stay, and 30-day mortality in the patients.

	Not occurred, n (%)	Occurred, n (%)	Sensitivity (95%CI)	Specificity (95%CI)	+LR (95%CI)	−LR (95%CI)	Accuracy
Endotracheal intubation							
IPI>4	60 (95.2)	7 (25.9)	74.07 (53.7–88.9)	95.24 (86.7–99)	15.56 (5–48)	0.27 (0.1–0.5)	88.9
IPI≤4	3 (4.8)	20 (74.1)					
GCS>12	54 (85.7)	7 (25.9)	74.07 (53.7–88.9)	85.71 (74.6–93.3)	5.19 (2.7–9.9)	0.3 (0.2–0.6)	82.2
GCS≤12	9 (14.3)	20 (74.1)					
EICU stay							
IPI>7	29 (58)	4 (10)	90 (76.3–97)	58 (43.2–71.8)	2.14 (1.5–3.0)	0.17 (0.07–0.4)	72.2
IPI≤7	21 (42)	36 (90)					
GCS>14	27 (54)	3 (7.5)	92.5 (79.6–98.4)	54 (39.3–68.2)	2.01 (1.5–2.7)	0.14 (0.05–0.4)	71.1
GCS≤14	23 (46)	37 (92.5)					
30-day mortality							
IPI>4	58 (86.6)	9 (39.1)	60.87 (38.5–80.3)	86.57 (76.0–93.7)	4.53 (2.3–9.0)	0.45 (0.3–0.8)	80
IPI≤4	9 (13.4)	14 (60.9)					
GCS>12	55 (82.1)	6 (26.1)	73.91 (51.6–89.8)	82.09 (70.8–90.4)	4.13 (2.3–7.3)	0.32 (0.2–0.6)	80
GCS≤12	12 (17.9)	17 (73.9)					

EICU: emergency intensive care unit; +LR: positive likelihood ratio; -LR: negative likelihood ratio.

time predicted extubation failure in subjects after extubation[18]. In another study, the correlation of IPI monitoring with arterial blood gas values was evaluated in patients treated under invasive and non-invasive mechanical ventilation in ICU. In this study, a correlation was found between IPI's SpO_2 and $PetCO_2$ values and arterial blood gas saturation and $PaCO_2$ measurements. With these results, it has been reported that IPI monitoring, which is a non-invasive and continuous measurement method, can be preferred to blood gas monitoring, which is an invasive method in the follow-up of patients in ICU[19].

In our study, we compared the IPI with GCS in making ETI decisions in critically ill patients. When the AUC values of IPI and GCS were compared, 0.906 for IPI and 0.860 for GCS were calculated, and no significant difference was found

between the AUC values (p=0.413). According to the best cut-off values, sensitivity was 74.07% and specificity was 95.24% for IPI, and sensitivity was 74.07% and specificity was 85.71% for GCS and sensitivity values were similar. This showed us that IPI has an accuracy equivalent to GCS in the early prediction of respiratory failure and ETI indication in critically ill patients, and timely interventions to prevent the progression of these patients to respiratory failure.

In our study, we also evaluated the effectiveness of IPI in predicting the length of stay in the ICU and predicting the 30-day mortality of critically ill patients. According to the best cutoff values determined, the sensitivity and specificity of IPI in predicting 30-day mortality were similar to the sensitivity and specificity of GCS cutoff values.

Unlike previous studies, in our study, it was thought that evaluating the deterioration in vital parameters of critically ill patients with bedside monitoring and controlling the patient's breathing by timely ETI decision would be effective and sufficient in preventing secondary complications that may develop without delay in airway management. We believe that continuous respiratory monitoring with IPI can prevent delay in making ETI decisions in critically ill patients and therefore allow timely administration of appropriate treatments that can prevent complications associated with instabilities in our decision to follow up with an advanced airway strategy.

This study has some limitations. First of all, this study is a single-center study and its population was limited to adult patients presenting to the ED. In addition, trauma patients and patients who were sedated in the ED and connected to an invasive mechanical ventilator were excluded from the study. Second, since the study was an observational study, no intervention was made according to the IPI value. The third limitation is the requirement for special equipment for IPI monitoring. It was the first study to determine the role of IPI in determining ETI, although there is no literature to evaluate the reliability of IPI in ETI planning of critically ill patients.

CONCLUSION

The IPI monitoring provides an objective evaluation in the follow-up of critically ill patients and is predictive in deciding on timely ETI in the ED.

ETHICS APPROVAL

Approval was obtained from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital *(KAEK/2019.05.130).* It was conducted in compliance with the principles of the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

DS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RG:** Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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American Thyroid Association and Thyroid Imaging Reporting and Data System developed by the American College of Radiology: which one is better at predicting malignancy risk?

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SUMMARY

OBJECTIVE: The aim of this study was to compare the capacity of American Thyroid Association and Thyroid Imaging Reporting and Data System developed by the American College of Radiology in predicting malignancy risk of thyroid nodules and to verify which one is better at avoiding unnecessary fine needle aspiration.

METHODS: This was a cross-sectional study with 565 thyroid nodules, followed at a tertiary care hospital, in an iodine-replete area. Those were classified as American Thyroid Association and Thyroid Imaging Reporting and Data System developed by the American College of Radiology systems and stratified according to the Bethesda classification of fine needle aspiration. The values of sensibility, specificity, positive predictive value, and negative predictive value accuracy were calculated. Also, the percentage of unnecessary biopsies was presented.

RESULTS: The mean age of the individuals was 58.2±13.5 [26–90] years for benign nodules and 41.7±15.6 [23–66] years for malignant nodules (p=0.002). Regarding gender, 92.6% (n=150) of the individuals with benign nodules and 85.7% (n=06) with malignant nodules were females (p=0.601). For American Thyroid Association, 90.9% of sensibility, 51.4% of specificity, 52.6% of accuracy, 10.2% of positive predictive value, and 98.9% of negative predictive value were found. For Thyroid Imaging Reporting and Data System developed by the American College of Radiology, 90.9% of sensibility, 49.7% of specificity, 52.1% of accuracy, 9.9% of positive predictive value, and 98.9% of negative predictive value were found. .Notably, 12.3% of unnecessary fine needle aspiration were found in American Thyroid Association and 44.4% were found in Thyroid Imaging Reporting and Data System developed by the American College of Radiology.

CONCLUSION: Both Thyroid Imaging Reporting and Data System developed by the American College of Radiology and American Thyroid Association are able to predict the malignancy risk of thyroid nodules. Thyroid Imaging Reporting and Data System developed by the American College of Radiology was better at avoiding unnecessary fine needle aspiration.

KEYWORDS: Thyroid nodule. Fine-needle aspiration. Cross-sectional study.

INTRODUCTION

Thyroid nodules are a common clinical diagnosis. Its prevalence among randomly selected individuals varies from 19 to 68%[1,2]. Most of these nodules do not cause significant symptoms; therefore, the main challenge in the treatment is to discard malignancy[3,4].

The gold standard test for thyroid nodules evaluation is ultrasound[5,6], which identifies the suspicious ones that should be biopsied through fine needle aspiration (FNA). When FNA is well indicated, it reduces the number of individuals submitted to surgery due to benign diseases and allows the diagnosis of those with cancer[3,7]. However, unnecessary FNA leads to more investigative thyroid procedures and higher costs for the Brazilian public health system[8].

The mainly used risk stratification systems are obtained from the American Thyroid Association (ATA)[9] last actualized in 2015 and the Thyroid Imaging Reporting and Data System developed by the American College of Radiology (ACR-TIRADS)[10] from 2017, since they provide an effective malignancy risk stratification[11,12]. Worldwide, the studies comparing these systems concluded that ACR-TIRADS leads to fewer unnecessary biopsies[13,14].

Only two Brazilian studies on this subject were found[15,16]. Neither of them finds relevant differences between ATA and ACR-TIRADS. Furthermore, Macedo[15] did not consider the most recent ACR-TIRADS classification and Rosario[16] only evaluated nodules with indeterminate cytology. Besides, they

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did not analyze which system is better at avoiding unnecessary FNA. Based on this context, this study aims to compare the capacities of ATA and ACR-TIRADS in malignancy-risk prediction[1] and verify which one is better at avoiding unnecessary FNA[2], especially in the Brazilian population, evaluated in the public health care system.

METHODS

Study design and participants

This is a cross-sectional study, developed at Santa Casa de Misericórdia de Belo Horizonte, a tertiary care hospital in an iodine-replete area, from January 2018 to October 2020. It follows the 196/96 National Health Board resolution and has obtained ethical approval from the Ethics and Research Committee (CAAE: 19375119.7.0000.5138). Informed consent was obtained from participants.

Data collection

Data were collected from the charts of individuals with thyroid nodules submitted to FNA following GE LOGIQ™ P9 ultrasonography. The criteria for FNA were based on the expertise of the attending physician and it was not evaluated in our study (patients were recruited after FNA). To reduce bias, all nodules were evaluated by the same pathologist. Location, size, composition, echogenicity, shape, margin, and vascularization were used to classify each nodule according to ATA and ACR-TIRADS.

ACR-TIRADS stratification ranges from 1 (benign – 0 points), 2 (not suspicious – 2 points), 3 (mildly suspicious – 3 points), 4 (moderately suspicious – 4-6 points) to 5 (highly suspicious – 7 or more points). Nodules are scored according to their composition, echogenicity, shape, margin, and echogenic foci[10]. ATA stratification also ranges from ATA 1 (benign), 2 (very low suspicion), 3 (low suspicion), 4 (intermediate suspicion) to ATA 5 (highly suspicious). The following patterns were considered suspicious: irregular margins, microcalcifications, taller than wide shape, disrupted rim calcifications with small extrusive hypoechoic soft tissue components, and evidence of extrathyroidal extension[9].

To compare these systems, ATA and ACR-TIRADS were separated into four groups according to the prediction of the risk of malignancy of the classification systems. Nodules that were classified as ACR-TIRADS 1, 2, and 3 and ATA 1 (benign), 2 (very low suspicion), and 3 (low suspicion) were considered to have low suspicion for malignancy. Nodules that were classified as ACR-TIRADS 4 and 5, and ATA 4 (intermediate suspicion), 5 (high suspicion), and 6 (indeterminate) have high suspicion of malignancy. It is crucial to point out that ATA does not classify isoechoic or hyperechoic nodules with malignant features (microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape). These nodules could be malignant in almost 20% of the cases, hence classifying them to have high suspicion of malignancy[10,11,12,14,15], which was done based on the previous rate of malignancy predicted by the classification systems[9,10].

Following the classification, the nodules went through FNA and the cytological results were classified into the Bethesda system. Bethesda II nodules were considered benign while Bethesda V and VI were considered malignant[16]. Nodules with incomplete description or not classified by the Bethesda system were excluded.

Unnecessary fine needle aspiration

Unnecessary FNA nodules were considered with benign cytology (Bethesda II) punctioned without indication from ACR-TIRADS and ATA or with indication from only one of the systems, resulting in benign cytology (Bethesda II).

Evaluated outcomes

Our primary outcome was to verify the capacity of ATA and ACR-TIRADS in malignancy assessment, by calculating sensibility, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

The second outcome was to verify the capacity of ATA and ACR-TIRADS guidelines in avoiding unnecessary FNA. Hence, only the nodules classified as Bethesda II, V, and VI were selected and evaluated retrospectively how they were stratified by ATA and ACR-TIRADS. Bethesda I, III and IV nodules were not included in the analysis due to the impossibility of assigning its behavior. These nodules are still being followed and a new analysis will be performed properly.

Data analysis

Quantitative data were summarized using exploratory analysis. Categorical data were presented in absolute frequency and percentage. Quantitative data were presented in mean±standard deviation. The age of participants was analyzed by the Kolmogorov-Smirnov test with normal distribution and compared by the t-test. Chi-square test was used to compare categorical variables and outcomes. When necessary, Fisher's exact test and Monte Carlo simulation were used. The analysis was made by the SPSS 20 software.

RESULTS

A total of 565 consecutive nodules submitted to FNA were analyzed, of which 35 were excluded due to a lack of ultrasound

data or nodule stratification. In sum, 169 nodules were included: 30.5% (n=162) benign (Bethesda II) and 1.3% (n=07) malignant (Bethesda V or VI). The remaining 364 nodules, divided into Bethesda I (n=273), Bethesda III (n=68), and Bethesda IV (n=23), were not included due to the lack of anatomopathological confirmation. About 7.1% (12/169) of nodules could not be classified by ATA, all being Bethesda II. This happened because ATA does not classify isoechoic or hyperechoic nodules with microcalcifications, irregular margins, extrathyroidal extension, or diameter taller than wide. However, they were included in our study because they can be classified by ACR-TIRADS.

From the individuals comprehended, the mean age was 58.2±13.5 [26–90] years for benign nodules and 41.7±15.6 [23–66] years for malignant nodules, with p=0.002. Concerning the gender, 92.6% (n=150) of the individuals with benign nodules and 85.7% (n=06) with malignant nodules were females (p=0.435). There was no significant difference between gender and final diagnosis.

The nodule's locations, characteristics, and the presence or absence of suspicious lymph nodes are described in Table 1. The factors related with a greater risk of malignancy were <1 cm size, hypoechogenicity, extra thyroid extension, irregular margins, and presence of calcifications.

According to Table 2, the majority of the nodules were classified as ACR-TIRADS 1–3 and ATA 1–3 (benign), and the classifications were able to discriminate into malignant and benign nodules as seen by p-value. The nodules classified as ATA 6 (non-classified) were included in the ATA 4 and ATA

Table 1. Analysis of the ultrasonographic characteristics of nodules.

Variables	Final diagnosis		Total	Risk of malignancy (%)	p-value
	Benign	Malignant			
Composition					
Pred. cistic	6 (3.3%)	0 (0.0%)	6 (3.1%)	0.0%	0.606
Pred. solid	63 (34.8%)	2 (18.6%)	65 (33.9%)	3.2%	
Mixed	25 (13.8%)	0 (0.0%)	25 (13.0%)	0.0%	
Spongiform	4 (2.2%)	0 (0.0%)	4 (2.1%)	0.0%	
Solid	83 (45.9%)	9 (81.8%)	92 (47.9%)	10.8%	
Echogenicity					
Anechoic	7 (3.9%)	0 (0.0%)	7 (3.6%)	0.0%	**0.039**⁺
Hyperechoic or isoechoic	98 (54.1%)	2 (18.2%)	100 (52.1%)	2.0%	
Hypoechoic	71 (39.2%)	9 (81.8%)	80 (41.7%)	12.7%	
Very hypoechoic	5 (2.8%)	0 (0.0%)	5 (2.6%)	0.0%	
Shape					
Taller-than-wider	8 (4.4%)	0 (0.0%)	8 (4.2%)	0.0%	0.476*
Wider-than-taller	173 (95.6%)	11 (100%)	184 (95.8%)	6.4%	
Margin					
Smooth or ill-defined	161 (89.0%)	5 (45.5%)	166 (86.5%)	3.1%	**0.003**
Lobulated or irregular	13 (7.2%)	4 (36.4%)	17 (8.9%)	30.8%	
Extrathyroidal extension	7 (3.9%)	2 (18.2%)	9 (4.7%)	28.6%	
Echogenic Foci					
None calcifications	161 (89.0%)	5 (45.5%)	166 (68.5%)	2.1%	**<0.001**
Macrocalcifications	13 (7.2%)	4 (36.4%)	17 (8.9%)	30.8%	
Microcalcifications	7 (3.9%)	2 (18.2%)	9 (4.7%)	28.6%	
Suspicious lymph nodes					
Yes	6 (3.3%)	2 (18.2%)	8 (2.4%)	33.3%	0.069
No	175 (96.7%)	9 (81.9%)	184 (95.8%)	5.1%	

Pred.: predominantly. Source: elaborated by the author. *Fisher test; ⁺Chi-squared test.

Table 2. Risk of malignancy for American Thyroid Association and Thyroid Imaging Reporting and Data System developed by the American College of Radiology classifications.

Classification	Final diagnosis		Total	Risk of malignancy (%)	p-value
	Benign	Malignant			
TIRADS 1–3	90 (49.7%)	1 (9.1%)	91 (47.4%)	1.1%	**0.009**
TIRADS 4–5	91 (50.3%)	10 (90.9%)	101 (52.6%)	11%	
ATA 1–3	93 (51.4%)	1 (9.1%)	94(49%)	1.1%	**0.010**
ATA 4–6	88 (48.6%)	10 (90.9%)	98 (51%)	11.4%	

ATA 1: benign nodule; ATA 2: very little suspicion; ATA 3: little suspicion; ATA 4: intermediary suspicion; ATA 5: high suspicion; ATA 6: non-classified. Source: elaborated by the author.

Table 3. Sensibility, specificity, accuracy, positive predictive value, and negative predictive value of American Thyroid Association and Thyroid Imaging Reporting and Data System developed by the American College of Radiology.

Parameters	ATA	ACR-TIRADS
Sensibility	90.9%	90.9%
Specificity	51.4%	49.7%
Accuracy	52.6%	52.1%
PPV	10.2%	9.9%
NPV	98.9%	98.9%

PPV: positive predictive value; NPV: negative predictive value. Source: elaborated by the author.

5 categories because their risk of malignancy are more close to these ATA categories in previous studies[11-13,16-18].

As seen in Table 3, sensibility and NPV were similar in both classifications. Furthermore, specificity, accuracy, and PPV from both systems were similar, but slightly higher in ATA.

Concerning the FNA's, ACR-TIRADS pointed to 44.4% (72/162) of punctions as unnecessary, in comparison to ATA, with 12.3% (20/162), p<0.001, which means that less nodules would be involved in a procedure if only ACR-TIRADS were used.

DISCUSSION

In this study, the capacity of ACR-TIRADS and ATA systems at predicting malignancy risk in thyroid nodules was compared. In addition, the capacity of these systems at avoiding unnecessary biopsies was investigated. According to the ATA and ACR-TIRADS classifications[10,11], nodules with <1 cm with ultrasound malignant characteristics could be submitted to FNA according to clinical judgment. The nodules with this condition in this study with FNA indicated were classified as high or intermediate ultrasound suspicion, showing that the clinical judgment of the physician was important. In our study, we had 15 nodules with <1 cm, and all of them had high or intermediate ultrasound suspicion. This demonstrates that the physician's clinical judgment was important to indicate the FNA.

Nonetheless, other two studies[19,20] found opposite results, with ATA's sensitivity being higher than ACR-TIRADS' (80–82 vs 48.9–76%) and ACR-TIRADS' specificity being higher than ATA's (60.6–97.5 vs 53.5–96.3%). However the values are quite close, concluding that both systems can effectively predict malignancy risk.

In this study, the mean age of individuals with malignant nodules was lower than the benign ones, which is supported by the findings in other studies that evaluate predictive features for malignancy[21,22]. In accordance with our results, other studies also did not find differences in gender[21].

The values of sensitivity and NPV were similar in both classifications and comparable to those obtained in another Brazilian study[15]. Specificity, accuracy, and PPV were similar but slightly higher in ATA, as the results shown by Cheng et al.[7], in which ATA presented a higher specificity and NPV. In agreement, a study[12] showed that the ATA guidelines yielded a significantly higher specificity (79.6 vs. 71.5%), while ACR-TIRADS had a higher sensitivity (83.2 vs. 77.3%). Thus, both systems could be used for nodule evaluation, without any significant difference in diagnosis.

On the contrary, our study found that ACR-TIRADS is better at avoiding unnecessary FNA, which could be used as selection criteria. This result is in accordance with Grani et al.[13], in which ACR-TIRADS allowed the higher reduction of biopsied nodules (268/502; 53.4%), which was significantly higher than ATA (220/502; 43.8%). The number of benign nodules biopsied using ACR-TIRADS (31.9–47.1%) was also smaller compared to ATA (69.3–78.1%) in two studies[14,20]. Hence, ATA tends to indicate FNA in smaller nodules than ACR-TIRADS, leading to more procedures.

It is relevant to mention that studies about this topic are scarce in Brazil and only two studies were found[15,16]. Considering that

Brazil is an enormous country with a high population diversity, results obtained from international studies such as those in Singapore[5], Italy[12], and Turkey[18,19] cannot be fully validated, reinforcing the necessity of new research. Our study has shown that both systems are effective at helping health professionals to indicate who should undergo biopsies procedures. Hence, the choice of use should be considered with other factors such as examiner skills and resources' availability. In this matter, ACR-TIRADS is found to be better at avoiding unnecessary biopsies, a strong advantage when considering that Brazil's ground health system is public, and supplies are often deficient[9].

Nevertheless, this study has potential limitations. In previous studies[10-12,14,15], the malignancy risk in ATA in non-classified nodules was around 20%. In this study, this could not be possible due to the small number of malignant nodules found (n=7) and because Bethesda I, III, and IV were excluded from the final analysis. Additionally, a higher number of Bethesda I nodules were included in this sample, when compared to that presented in most studies, roughly 15% of Bethesda I nodules[15], explained by the difficulty in maintaining the individuals' follow-up throughout COVID-19 pandemic and due to the high number of nodules with <1 cm submitted to FNA. Furthermore, Bethesda III and IV nodules, considered of indeterminate cytology, were excluded. Due to the pandemic, the second FNA biopsy of these nodules and the surgery were delayed, when indicated and the findings could not be included here. Hence, data will be updated after these procedures and published soon in another article. Another limitation is that the final diagnoses in our study were based on the cytopathology, which can cause false negatives and false positives when compared with the surgical histology. The probability of a false diagnosis in Bethesda II and Bethesda V is very low, varying from <3 and <1%, respectively, when compared with histopathology[20]. Also, the low number of malignant nodules could be due to the exclusion of Bethesda III and IV. Moreover, our study tended to suffer from a selection bias because all FNAs were indicated by multiple professionals following different criteria that are not specified in the individual's charts.

CONCLUSION

We found that ACR-TIRADS and ATA are equally capable of predicting malignancy risk at the same level, presenting similar results in every evaluated aspect (sensibility, specificity, PPV, NPV, and accuracy). Despite that, our study found that ACR-TIRADS was better at avoiding unnecessary FNAs, making it a better choice for our public health system. Future studies in the Brazilian population with a higher number of nodules may be conducted, including those with indeterminate cytology.

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AUTHORS' CONTRIBUTIONS

MNA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **JRC:** Conceptualization, Writing – original draft, Writing – review & editing. **LMS:** Conceptualization, Writing – original draft, Writing – review & editing. **LFGGM:** Conceptualization, Writing – original draft, Writing – review & editing. **RFO:** Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **MCBÁ:** Formal Analysis, Investigation, Methodology. **FCPM:** Conceptualization, Data curation, Formal Analysis, Project Administration, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Maternal near miss: before and during the coronavirus disease 2019 pandemic

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate and compare Maternal Near Miss prevalence and outcomes before and during the coronavirus disease 2019 pandemic.

METHODS: This retrospective study was carried out in a university maternity hospital of high complexity. The population was divided into two groups: G1, 1 year before the coronavirus disease 2019 pandemic period (August 2018–July 2019) and G2, 1 year during the pandemic period (August 2020–July 2021). All pregnant/postpartum women hospitalized up to 42 days after the end of pregnancy/childbirth were included, and pregnant women who were admitted with coronavirus disease 2019/flu symptoms were excluded. The association of variables with "Maternal Near Miss" was estimated using logistic regression.

RESULTS: A total of 568 women from G1 and 349 women from G2 fulfilled the Maternal Near Miss criteria. The prevalence of Maternal Near Miss in pre-pandemic was 144.1/1,000 live births and during the pandemic was 78.5/1,000 live births. In the analysis adjusted for G1, the factors of days of hospitalization (PR: 1.02, CI: 1.0–1.0, p<0.05), pre-eclampsia (PR: 0.41, CI: 1.4–2.2, p<0.05), and sepsis/severe systemic infection (PR: 1.79, CI: 0.3–0.4, p<0.05) were crucial for women with the Maternal Near Miss condition to have a greater chance of being admitted to the intensive care unit. In G2, low education (PR: 0.45, CI: 0.2–0.9, p<0.05), eclampsia (PR: 5.28, CI: 3.6–7.6, p<0.05), and use of blood products (PR: 6.48, CI: 4.7–8.8, p<0.05) increased the risk of admission to the intensive care unit.

CONCLUSION: During the pandemic, there was a lower prevalence of Maternal Near Miss in high-risk pregnancies, fewer hospitalizations, and more deaths compared to the non-pandemic period.

KEYWORDS: Pregnancy complications. Near miss, healthcare. COVID-19 pandemic.

INTRODUCTION

The COVID-19 pandemic contributed to increased morbidity and mortality among pregnant women. COVID-19 positive pregnant women are more likely to develop hypertension/pre-eclampsia and eclampsia. Notably, 1 in every 68 affected women require intensive care and has 22 times higher risk of mortality[1,2].

Worldwide, governments and public health surveillance leaders emphasized the need for people to visit hospitals only when necessary to mitigate the risk of exposure to COVID-19 infection and to avoid overcrowding of health facilities[3]. Current studies suggest that social isolation adopted as a security measure against the pandemic could have contributed to pregnant women not seeking regular health services[4,5].

There was a sharp reduction in reporting of non-COVID-19 cases[3,6], as well as in obstetric emergency services[5]. This restriction on access to healthcare may be associated with significant clinical implications for pregnant or postpartum women, such as the Maternal Near Miss (MNM)[7]. Additionally, there were uncertainties related to the outcome of COVID-19 infection during pregnancy.

Therefore, relevant public agencies and health institutions were concerned, as many high-acuity patients, who needed emergency care, did not attend services due to the fear of contamination. Recent studies show that delays in timely care for pregnant women have increased maternal morbidity and mortality[4,7,8].

Studies indicate that COVID-19 positive pregnant women have similar outcomes as non-pregnant women[8,9], but show higher mortality in the infected group. However, there is still no measurement of the actual impact of the SARS-CoV-2 pandemic on pregnant women's social and health aspects or puerperium. Thus, this study aims to evaluate and compare MNM prevalence and outcomes before and during the COVID-19 pandemic.

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METHODS

This hospital-based study was performed following the guidelines and checklist of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[10]. This study was carried out in a university maternity hospital of high complexity that attends high-risk pregnant women in Brazil, with an annual cesarean delivery rate of approximately 62%.

The population was selected by review of medical records during two periods: the first one from August 2018 to July 2019 (before the COVID-19 pandemic: G1) and the second period comprised the interval from August 2020 to July 2021 (during the pandemic period: G2). In both periods, the same months were chosen before and during the pandemic to reduce the seasonal effects of other pathologies and provide greater similarity between the periods.

All pregnant or postpartum women admitted to the high-risk ward of the health institution up to 42 days after the end of pregnancy or childbirth were included, regardless of gestational age. MNM was identified using the criteria of the World Health Organization (WHO). Patients who have entered COVID-19 or flu symptoms were excluded. This exclusion is justified by the fact that pregnant women undergoing treatment for COVID-19 used medications (e.g., corticosteroids) that could interfere with hemodynamic balance, thus causing accuracies in the diagnosis of MNM.

Data collection was performed by two research assistants trained to use the tool mentioned above and an established form to collect sociodemographic information, obstetric history, and current obstetric conditions presented at the time of the woman's admission to the institution.

Statistical analysis was performed using the Stata software, version 14, with a significance level of 5% assigned to all statistical tests ($p<0.05$). To calculate the MNM prevalence ratio (PR) in both periods, we used the total number of MNM cases; in the denominator, we used the number of live births (LB) during the research period with a 95% confidence interval (CI). The chi-square test (χ^2) was used to compare the groups, before and during the pandemic. Mann-Whitney test was performed for intergroup comparisons. The logistic regression was performed after the bivariate analysis, and the "adjrr" command from the Stata software, version 14, was used to transform the odds ratios into PRs. A final regression analysis was performed with the variables that presented a p-value<0.05 in the bivariate analysis that served to perform the adjusted PR and respective CI of the women in both groups who were admitted to the intensive care unit (ICU).

Ethics

The research was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte CAAE: 16946919.7.0000.529. This study was conducted in accordance with the Declaration of Helsinki and its modifications.

RESULTS

One year before the pandemic, 2,740 high-risk obstetric hospitalizations were identified, and during the pandemic, it was 1723. Regarding MNM, we selected all women who presented at least one MNM criteria listed by the WHO: 568 women in the period corresponding to 1 year before the pandemic and 349 women during the pandemic (Figure 1).

Prevalence of maternal near miss

The results show an MNM prevalence of 144.1/1000 LB 1 year before the pandemic and 78.5/1000 LB during the pandemic. A total of 3939 cases were identified in the year before the pandemic and 4445 during the pandemic.

Sociodemographic and obstetrics determinants

Significant differences between the groups were identified for the variables of age (28.7 vs. 30.3; p=0.01), race/color (p=0.02), and stable union (p=<0.01). This indicated that women hospitalized in G2 had greater age, most considered themselves of mixed race, and they declared a stable union compared to those hospitalized in G1 (Table 1).

Regarding obstetric aspects, differences between groups were observed in terms of the number of pregnancies (2.3 CI=2.2–2.5 vs. 2.7, CI=2.6–3.0) and mode of delivery cesarean (85.2 vs. 70.5% p=<0.01). The data indicate a lower frequency of cesarean delivery during the pandemic compared to the previous year. Additionally, the average gestational age of the pandemic group was lower (36 vs. 35 gestational weeks).

Moreover, there was a difference in the period of hospitalization, indicating that G2 had a shorter hospital stay than G1 (8 days vs. 9 days, p=<0.01). We also identified that in G1, 80.3% of the women underwent prenatal care compared to 77.3% in G2. However, 85% of the population studied took up to six prenatal consultations in both groups.

Identification of maternal near miss

Regarding the identification conditions of MNM to the symptoms criterion, a relevant frequency of women diagnosed with pre-eclampsia in both groups is perceived (G1=67.7% vs. G2=95.7%). In terms of the clinical interventions item,

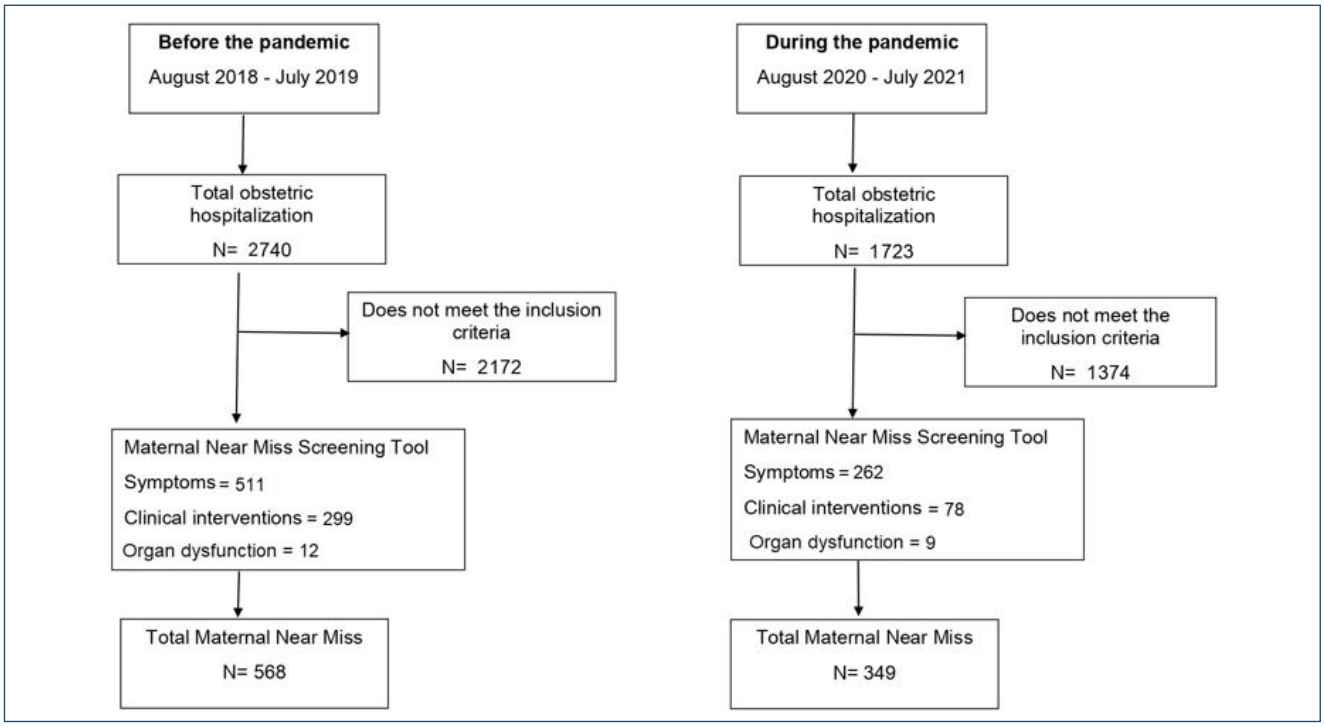

Figure 1. Sample selection flowchart.

the use of blood products was higher in G1 (12.3 vs. 4.3%). However, uterine complications were more frequent in G2 (1.2 vs. 0.9%) (Table 1).

In the adjusted analysis, the factors such as days of hospitalization (PR: 1.0201, 95%CI=1.0099, 1.0304), pre-eclampsia (PR: 0.4125, 95%CI=0.3453, 0.4928), and sepsis/severe systemic infection (PR: 1.7940, 95%CI: 1.4222, 2.2630) were decisive for women with the MNM condition to be more likely to be admitted to the ICU in G1. In G2, low schooling (incomplete high school) (PR: 0.4560, 95%CI=0.2202, 0.9446), eclampsia (PR=5.2814, CI 95%=3.6225, 7.6999), and use of blood products (PR: 6.4856, CI 95%=4.7687, 8.8205) increased the risk of ICU admission (Table 2).

DISCUSSION

This study identified a lower number of obstetric hospitalizations and prevalence of MNM during the COVID-19 outbreak compared to the same period of the previous year.

Women hospitalized during this pandemic had a mean gestational age of 35 weeks at admission, had fewer prenatal consultations, remained hospitalized for a shorter time, and had higher mortality rate (>150%, i.e., 20.5 times higher). Additionally, both groups presented the most frequent cesarean delivery and the diagnosis of eclampsia as a criterion for symptoms of MNM.

Uncertainties about the virus, maternal and neonatal outcomes, and constant changes in COVID-19 guidelines may have resulted in fewer visits to the emergency room and reduced MNM prevalence compared to the previous year[4,5,11,12]. Despite that, there were no recommendations to stop the care or monitoring of pregnant and postpartum women in the guidelines issued by health institutions of many countries[13].

Our data agree with a study by Kugelman et al. in an obstetric emergency room in Israel, which showed that fewer patients visited the obstetric emergency room. The most frequent diagnosis was "active labor"[4]. Another study by Abdollahpour et al. showed that the prevalence of MNM globally was 18.67/1000 LB based on the WHO criteria. According to our result (78.0/1000 LB), the prevalence was reduced during the pandemic. However, comparing global and local values, we identified a need to improve care for pregnant women[14].

Regarding MNM, our data showed that pre-eclampsia frequently occurred in both periods. This result was expected as the research was conducted in a high-risk maternity hospital.

These findings align with the results obtained from a multinational cohort study involving 2130 pregnant women in 18 countries. The results showed higher rates of adverse outcomes, including eclampsia and preterm birth, in pregnant women during the pandemic[1]. Additionally, we can infer that the period of social isolation could have influenced the prevalence of hypertensive disorders because pregnant women

Table 1. Comparisons of sociodemographic, obstetrics, and Maternal Near Miss criteria between groups: 1 year before the pandemic (G1) and during the pandemic (G2).

Variables	Group 1 (568)		Group 2 (349)		p-value
	N	%	N	%	
Average age	28.7		30.3		0.01
Education					
1st degree incomplete	196	36.2%	128	38.2%	0,31
1st degree complete	31	5.7%	22	6.6%	
2nd degree incomplete	64	11.8%	41	12.2%	
2nd degree complete	191	35.3%	116	34.6%	
Incomplete higher	20	3.7%	6	1.8%	
Graduated	39	7.2%	22	6.6%	
Race/color					
White	28	4.9%	6	1.7%	0.02
Black/Brown	539	95%	342	98%	
Yellow	0	0.0%	1	0.3%	
Marital status					
Not married	184	34.8%	104	29.8%	<0.01
Married	168	31.8%	93	26.6%	
Separated	2	0.4%	2	0.6%	
Stable union/Others	175	33.1%	150	43%	
Mean number of pregnancies	2		2		0.01
Abortion	132	23.3%	88	25.9%	0.38
Average Gestational Age	36		35		0.67
Prenatal	416	80.3%	262	77.3%	0.30
Six prenatal consultations	445	80.3%	289	85.2%	0.79
Average days of hospitalization	9		8		<0.01
Way of delivery					
Vaginal	46	8.1%	31	8.9%	<0.01
Cesarean	483	85.2%	246	70.5%	
Did not give birth	38	6.7%	68	19.5%	
IUFD[a]	0	0.0%	2	0.6%	
Stillborn[b]	0	0.0%	2	0.6%	
Maternal death	2	0.3%	5	1.4%	0.05
Symptom-based MNM criteria					
Eclampsia	63	11.1%	20	5.7%	0.01
Pre-eclampsia	384	67.7%	286	81.9%	<0.01
Sepsis/severe systemic infection	37	6.5%	15	4.3%	0.19
Hemorrhage	25	4.4%	27	7.7%	0.04
Uterine rupture	1	0.2%	1	0.3%	0.99
Intervention-based MNM criteria					
Used Hemoderivatives	70	12.3%	15	4.3%	<0.01
Laparotomy	14	2.5%	3	0.9%	0.12
ICU[c] admission	284	50.1%	60	17.2%	<0.01
Organ dysfunction based MNM criteria*					
Cardiovascular	1	0.2%	2	0.6%	0.56
Respiratory	1	0.2%	2	0.6%	0.56
Renal	2	0.4%	2	0.6%	0.99
Neurological	1	0.2%	0	0.0%	0.99
Uterine[d]	7	1.2%	3	0.9%	0.75

[a]IUFD: intrauterine fetal death; [b]Stillborn: death of a fetus in utero after 20 weeks of gestation. [c]ICU: Intensive care unit; [d]Uterine: Characterized by hemorrhage, (postpartum vaginal bleeding of 1000 ml or more in volume) or uterine infection leading to hysterectomy. Missing data in Group 1 (Education=27; Race/color=1; Marital status 39; Abortion=2; and Prenatal=6). Missing data in Group 2 (Education=14; Abortion=4; and Prenatal=6). *There were no cases of Hematological and Hepatic in both groups.

Table 2. Analysis logistic regression of determinants for intensive care unit admission of women in groups: 1 year before the pandemic (G1) and during the pandemic (G2).

Characteristics	Group 1				Group 2			
	PR	(95%CI)	PR adjusted	(95%CI)	PR	(95%CI)	PR adjusted	(95%CI)
Gestational age	0.99	(0.9–0.9)*	0.99	(0.9–1.0)	1.01	(0.9–1.0)	0.99	(0.9–1.0)
Hospitalization days	1.03	(1.0–1.0)*	1.02	(1.0–1.0)*	1.03	(1.0–1.0)*	1.01	(0.9–1.0)
Education								
2nd degree incomplete	1.14	(0.9–1.4)	1.08	(0.8–1.3)	0.68	(0.2–1.6)	0.45	(0.2–0.9)*
Eclampsia	1.83	(1.5–2.1)*	0.96	(0.7–1.2)	5.48	(3.7–7.9)*	5.28	(3.6–7.6)*
Pre-eclampsia	0.37	(0.3–0.4)*	0.41	(0.3–0.4)*	0.49	(0.2–1.0)	1.15	(0.3–3.8)
Sepsis/severe systemic infection	2.01	(1.7–2.2)*	1.79	(1.4–2.2)*	2.47	(1.2–4.8)*	1.21	(0.4–2.9)
Hemorrhage	1.46	(1.1–1.9)*	0.87	(0.5–1.4)	2.98	(1.8–4.8)*	0.70	(0.2–2.0)
Used hemoderivatives	1.94	(1.7–2.2)*	1.26	(0.8–1.8)	6.15	(4.4–8.5)*	6.48	(4.7–8.8)*
Laparotomy	0.99	(0.5–1.6)	0.36	(0.1–0.7)	3.97	(1.7–9.1)*	0.12	(0.0–0.8)
Uterine	1.14	(0.5–2.1)	0.70	(0.3–1.5)	3.97	(1.7–9.1)*	1.16	(0.1–9.7)
Way of delivery								
Cesarean	0.81	(0.6–0.9)*	1.01	(0.8–1.2)	1.25	(0.7–2.1)	1.18	(0.7–1.8)
Did not give birth	1.52	(1.2–1.8)*	1.05	(0.7–1.5)	0.72	(0.3–1.4)	0.87	(0.5–1.4)

*p<0.05.

stayed at home longer, favoring extended periods of rest[15,16]. Thus, the uncertainties increased stress and anxiety. A few studies show that these factors substantially contribute to weight gain and changes in blood pressure levels[17,18].

Our data showed that women hospitalized during the pandemic had shorter hospital stays. There may have been a need to reduce hospitalization to release beds[19,20]. Studies report that health institutions have made structural adaptations to meet the high demand caused by the pandemic. An observational study in the United States also identified reduced hospitalization time during the COVID-19 pandemic, and there was no change in readmission rates[21]. Additionally, a systematic review and Cochrane meta-analysis showed that no evidence could support the higher/lower probability of adverse events in the case of early discharge, especially in the postpartum period[22].

The adjusted logistic regression showed that pre-eclampsia and eclampsia were among the determining factors in increasing the probability of women being admitted to the ICU during the pandemic.

This study shows that pregnant/puerperal women in G1 who presented with pre-eclampsia were four times more likely to require ICU. Another critical condition was sepsis/severe systemic infection, which represented twice the likelihood of ICU admission for this group. However, in G2, women with eclampsia were five times more likely to be in ICU and six times more likely to use blood components. Thus, eclampsia is responsible for increasing the rates of maternal deaths and requires more severe clinical interventions such as the replacement of blood products[1,23,24].

Thus, the maternal death numbers presented in this study support the assumption that during the global spread of SARS-CoV-2, pregnant/puerperal women needed critical care. The number of maternal deaths was almost three times higher than the period, not the pandemic, since the delay in seeking care caused the aggravation of the clinical condition.

Despite promising findings, this study has limitations, such as no follow-up with these women after they left the hospital environment, which may contribute to underestimating the magnitude of MNM and the impacts of COVID-19 in this population.

CONCLUSION

The prevalence of MNM in high-risk pregnancies was lower during the worldwide spread of COVID-19. However, these results can be attributed to the reduction in the search for assistance, motivated by fear of contamination. Additionally, this study identified that a few triggering factors for MNM such as hypertensive disorders are preventable and treatable. It remains a challenge to fathom the overall damage inflicted by this

pandemic, which, apart from infecting people, caused significant changes in the flow of care to various population groups. Thus, it is necessary to rethink future guidelines and measures in cases of similar outbreaks to mitigate the possible damage to these populations.

AUTHORS' CONTRIBUTIONS

CLF: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ACS:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **KSM:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **AKG:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MEML:** Formal Analysis, Software. **YHSS:** Formal Analysis, Software.

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ORIGINAL ARTICLE

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Association of polycystic ovary syndrome with mammographic density in Turkish women: a population-based case-control study

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SUMMARY

OBJECTIVE: The objective of this study was to investigate the breast densities and Breast Imaging-Reporting and Data System scores of patients with polycystic ovary syndrome and normoovulatory women and to determine whether these patients constitute a high-risk population for breast cancer.

METHODS: This retrospective case-control study was conducted at our institution between January 2022 and December 2022, involving patients diagnosed with polycystic ovary syndrome. Menstrual periods, hyperandrogenemic findings, and ultrasound reports of the patients were retrieved from our hospital's database. Patients who met at least two of the Rotterdam criteria were included in the polycystic ovary syndrome group. A total of 70 premenopausal patients over the age of 40 years, diagnosed with polycystic ovary syndrome, and 70 normoovulatory women, matched for age and body mass index, were included in the study. The two groups were compared regarding age at menarche, menstrual pattern, gravida, parity, levels of follicle-stimulating hormone, luteinizing hormone, and estradiol, endometrial thickness, breast density category, and Breast Imaging-Reporting and Data System classifications.

RESULTS: Patients in the polycystic ovary syndrome group had a higher age at menarche (12.7 vs. 12.3, p=0.006). There was no difference between the gonadotropin levels in both groups. However, the estradiol level was higher in the polycystic ovary syndrome group (p<0.001). There was no statistically significant difference between the two groups in terms of breast density and Breast Imaging-Reporting and Data System scores (p=0.319 and p=0.650, respectively).

CONCLUSION: Although we can conclude that the risk of breast malignancy is not increased in patients with polycystic ovary syndrome, the impact of the complex hormonal status of polycystic ovary syndrome on breast cancer remains unclear in the literature.

KEYWORDS: Breast density. Breast neoplasms. Mammography. Menarche. Polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by hyperandrogenism, anovulation, and polycystic ovaries (PCOs), affecting approximately 5–10% of women of reproductive age[1]. The diagnosis of PCOS is based on the Rotterdam criteria, with oligo-anovulation defined as a menstrual cycle length of less than 35 days[2]. Although PCOS patients are categorized into different phenotypes, this classification remains a topic of debate[3].

PCOS patients often exhibit various metabolic changes, such as high body mass index (BMI), hyperandrogenism, and hyperinsulinemia[4].

Consequently, PCOS has been associated with an increased risk of several types of cancer[5].

The relationship between PCOS and breast cancer is intricate due to various factors that both elevate (e.g., first pregnancy at an advanced age) and reduce (e.g., late onset of menarche) the risk of breast cancer. Furthermore, obesity, which is common in PCOS, is also linked to cancer[6].

Several studies have examined the association between breast cancer and PCOS, but the results have been inconsistent[7,8].

Mammography is considered the gold standard screening method for early detection of breast cancer, significantly reducing breast cancer mortality. The current approach in mammography evaluation involves assessing the Breast Imaging-Reporting and Data System (BI-RADS) score within six categories and breast density within four categories, as outlined by the American College of Radiology (ACR) (Figures 1 and 2)[9].

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Mammographic density (MD) is a measurement used to describe the fibrous and glandular breast tissue, comprising epithelial tissue and stroma, observed on a mammogram[10].

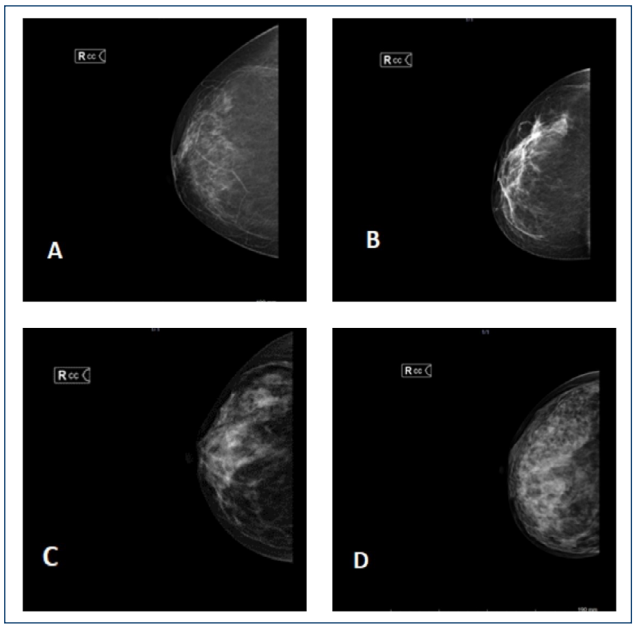

Figure 1. ACR BI-RADS classification for breast density.

Increasing MD serves as a valuable biomarker for breast cancer development. A meta-analysis demonstrated that women with an MD of at least 75% have a sixfold higher risk of developing breast cancer compared with those with an MD≤10%. A recent biological study conducted in 2018 revealed a higher transformation rate to malignant cells in dense breast tissue compared with non-dense tissue[11,12].

The objective of this study was to investigate the relationship between PCOS, high breast density, and an increased risk of breast cancer.

METHODS

This retrospective case-control study was conducted at our institution between January 2022 and December 2022, involving patients diagnosed with PCOS. PCOS was diagnosed according to the Rotterdam criteria: amenorrhea, clinical/biochemical hyperandrogenism, and PCOs on ultrasound and at least two of these criteria[5].

The database of our hospital was scanned, and the history of the patients, their menstrual status, hyperandrogenemic findings, and ultrasound reports were examined. Patients meeting at least two of these criteria were included in the PCOS group.

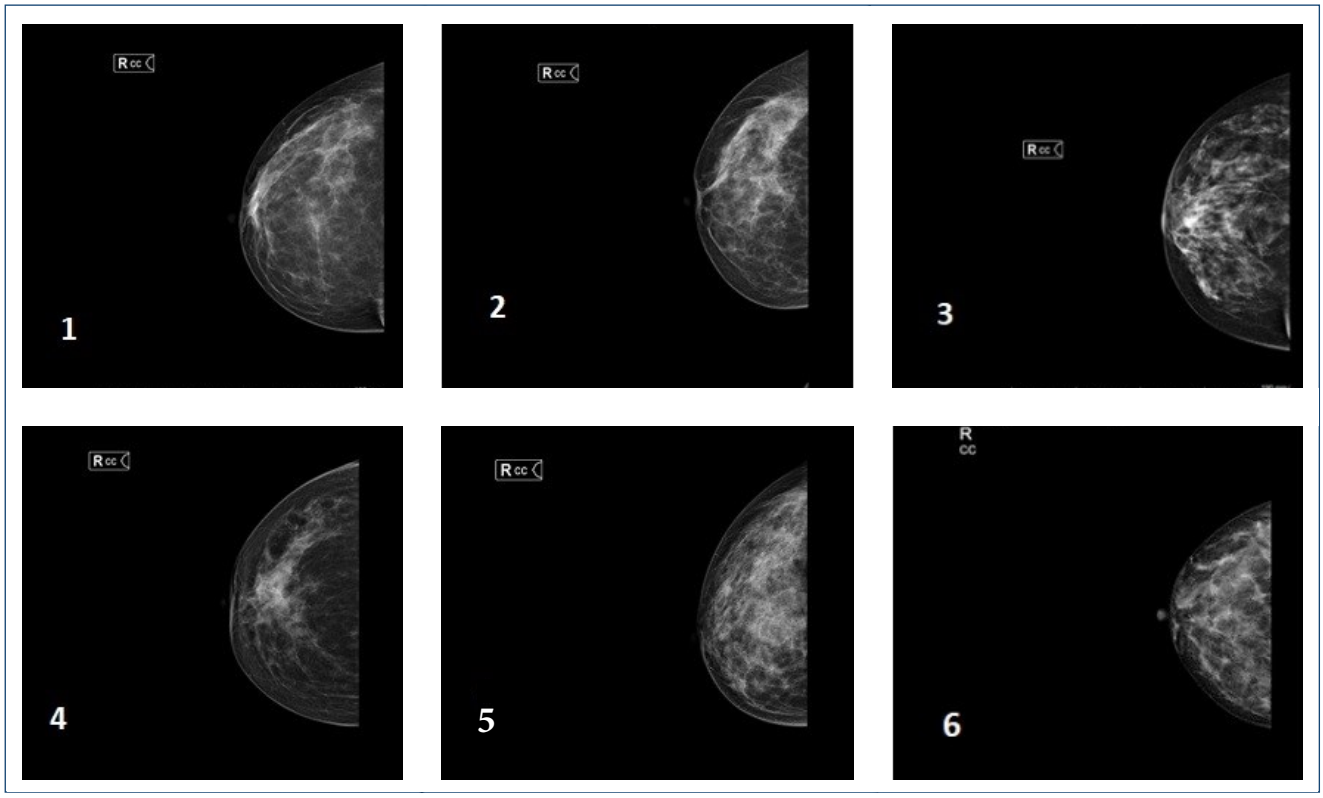

Figure 2. BI-RADS categorization.

A total of 70 PCOS and 70 normoovulatory women who had routine mammography in the premenopausal period and over the age of 40 years were included in the study. Mammograms are taken by the radiology technician in the hospital where the study is performed and interpreted by the radiologist. Two standard mediolateral-oblique and craniocaudal breast scans are routinely performed in our hospital with digital mammography for all patients aged 40 years and over. The study data were obtained from the hospital database by the researchers. Both groups were matched for age and BMI. Exclusion criteria were renal failure androgen-producing neoplasm, late-onset adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, breast surgery, and history of breast cancer.

All patients underwent mammography in the first half of the menstrual cycle, which was performed by radiology technicians with at least 10 years of experience. The BI-RADS is used to determine breast density. The final assessment includes the BI-RADS 0–6 categorization. A category assessment of BI-RADS 0 refers to an incomplete evaluation with further imaging, requiring additional mammographic views including spot compression or magnification and/or ultrasound. BI-RADS 1 refers to a negative examination, meaning that there are no masses, suspicious calcifications, or areas of architectural distortion. BI-RADS 2 is consistent with benign findings, including secretory calcifications, simple cysts, fat-containing lesions, calcified fibroadenomas, implants, and intramammary lymph nodes. BI-RADS 3 is probably benign and should have shortened interval follow-up to determine stability. Findings are a non-palpable, circumscribed mass on a baseline mammogram, a focal asymmetry, which becomes less dense on spot compression images, or a solitary group of punctate calcifications. BI-RADS 4 is a suspicious abnormality, representing the chance of being malignant (in percent). It is subdivided into a, b, and c. The subcategory of (a) has a low probability of malignancy with a 2–10% chance of malignancy. The subcategory of (b) has an intermediate change of malignancy ranging from 10 to 50%. The subcategory of (c) has a high probability of malignancy ranging from 50 to 95%. BI-RADS 5 is highly suggestive of malignancy more than 95%. The final category that was recently added is the BI-RADS 6, which is used for determining pathology-proven malignancy (Figure 2)[9].

The ACR BI-RADS is used for measuring breast density. ACR BI-RADS Atlas 2013 (version 5) is the updated version of the 2003 Atlas. It defines density as follows: (a) breasts are almost completely oily; (b) there are scattered areas of fibroglandular density; (c) heterogeneous density of breasts may hide small masses, and (d) excessive density of breasts reduces the sensitivity of mammography[9] (Figure 1).

Age, age at menarche, BMI, menstrual pattern, gravida, parity, estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels on the third day of menstruation, endometrial thickness measurements in the first 3 days of menstruation, BI-RADS classification scores and ACR breast density categories in mammography, and the presence of solid or cystic masses on breast ultrasound were scanned from computer-based hospital records (I.K). The data of the PCOS group and the normal group were compared.

Statistical analysis

According to a previous study, the number was calculated as 70 for each group with 80% power and 0.05 alpha error to detect the 25% difference between the two groups in breast density by using the Epi Info website (www.cdc.gov/epiinfo/)[13].

Frequency tables for categorical variables and descriptive statistics for continuous variables were calculated. The Shapiro-Wilk test of normality was used to examine whether the continuous data were normally distributed.

As the data were not normally distributed, continuous data in two independent groups (normoovulatory/PCOS) were compared with the Mann-Whitney U test. Categorical data were analyzed with the Pearson chi-square test for the presence/absence of PCOS. The significance was taken as 0.05 in all hypothesis tests. For statistical analysis, the IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp., Released 2017) program was used.

Statement of ethics

The ethics committee approval was obtained. The approval date is 29.12.2021, and the ethics committee decision number is 466. Due to the retrospective design of the study, it was not possible to obtain informed consent from the patients.

RESULTS

No significant difference was found between the group with PCOS (Group 1) and the group with normoovulatory women (Group 2), in terms of age, BMI, gravida, and parity. The mean menarche age of Group 1 was 12.7 years, while the mean menarche age of Group 2 was 12.3 years, which was statistically significant (p=0.006). Table 1 shows the demographic data.

When the endometrial thickness, FSH, and LH levels were compared, no statistically significant difference was found. The mean of E2 was found to be significantly higher in the PCOS group compared with the other group (p<0.001). There was no statistically significant difference between the two groups in terms of the presence of fibroadenoma and cystic mass in the

breast. When the ACR breast density category and BI-RADS score were compared, no statistically significant difference was found between the two groups (p=0.319 and 0.650, respectively). A comparison of study data by PCOS status is shown in Table 2.

DISCUSSION

Both epidemiological and experimental data suggest that the cumulative exposure of the mammary epithelium to estrogen unopposed by progesterone plays a role in breast cancer

Table 1. Demographic data.

	PCOS group/group 1 (n=70) (Mean±SD)	Normoovulatory group/group 2 (n=70) (Mean±SD)	P
Age (year)	42.6±3.7	42.2±3.2	0.230[a]
BMI (kg/m^2)	24.2±3.80	24.4±3.80	0.706[a]
Gravidity	2.6±1	2.5±0.9	0.358[b]
Parity	2.2±1.1	2.1±0.9	0.784[a]
Age of menarche (years)			
<12 years	7 (10%)	4 (5.7%)	0.006[b]
12–14 years	58 (82.8%)	59 (84.3%)	
≥14 years	5 (7.2%)	7 (10%)	

[a]Mann-Whitney U test, and [b]chi-square test; BMI: body mass index.

Table 2. Comparison of study data by polycystic ovary syndrome status.

	PCOS group/group 1 (n=70) (Mean±SD)	Normoovulatory group/group 2 (n=70) (Mean±SD)	p
Endometrial thickness (mm)	6.5±2.8	7±2.6	0.128[b]
FSH (mIU/mL)	12.4±11.05	13.1±11.6	0.687[b]
LH (mIU/mL)	16.1±12.03	13.5±12.4	0.802[b]
Estradiol (pg/mL)			
0–40 pg/mL	(7) 10%	(41) 58.6%	**<0.001[c]**
40–80 pg/mL	(11) 15.7%	(18) 25.7%	
≥80 pg/mL	(52) 74.3%	(11) 15.7%	
ACR breast density (n %)			
A	(3) 4%	(9) 12%	0.319[b]
B	(21) 30%	(18) 26%	
C	(39) 56%	(35) 50%	
D	(7) 10%	(8) 12%	
BIRADS (median)	1	2	0.650[b]
BIRADS 1 (n%)	(16) 22.9%	(21) 30%	
BIRADS 2 (n%)	(32) 45.7%	(26) 37.1%	
BIRADS 3 (n%)	(20) 28.6%	(19) 27.2%	
BIRADS 4 (n%)	(1) 1.4%	(1) 1.4%	
BIRADS 5 (n%)	(1) 1.4%	(1) 1.4%	
BIRADS 6 (n%)	0	(2) 2.9%	
Presence of cystic mass in the breast[a]	50%	64.3%	0.088[c]
Cyst size in the breast (mm)	8.8±6.6	7.9±6.1	0.665[b]
Presence of fibroadenoma in the breast[a]	8.60%	18.60%	0.084[c]
Fibroadenoma size (mm)	9.2±3.6	9.4±5.1	0.691[b]

[a]n (%), [b]Mann-Whitney U test, and [c]chi-square test; BMI: body mass index. Bold indicates statistically significant p-value.

development[14]. While planning our study, we set out with the idea of whether this unopposed estrogen status, which is mostly seen in PCOS, affects breast density and BI-RADS scores and therefore breast cancer risk.

Although there are studies in the literature on whether PCOS increases the risk of breast cancer or not, a common conclusion has not been reached[15-20].

In our study, we used the evaluation of ACR breast density and BI-RADS in mammography, which is accepted as one of the best detection methods of breast cancer risk. However, the most important thing is to raise awareness of women on this issue and to facilitate access to health services for women with symptoms[21].

The normoovulatory women group and the group with PCOS have no significant difference in terms of age distribution, BMI, gravida, and parity, and the two groups were homogeneous in terms of these data. There are results in the literature that obesity increases the risk of especially estrogen receptor (ER)-positive breast cancer[22,23]. In our study, the homogeneity of the BMI index between the two groups excluded the obesity factor.

Although there are studies showing that hormonal factors affect the endometrium in PCOS patients[24], we did not find a significant difference in endometrial thickness between the two groups as a result of our study. There is no difference between the two groups in terms of FSH and LH levels. When E2 levels were compared, E2 levels of Group 1 patients were found to be significantly higher, as expected in the PCOS clinic.

In the literature, very different results have been suggested regarding breast density and breast cancer risk in PCOS patients, which is the main starting point of our study. In the literature, Mendelian randomized studies have shown that the risk of ER-positive breast cancer is increased in PCOS in particular[15,20].

A retrospective cohort study showed that the most common cause of death in PCOS patients was breast cancer, but there was no evidence that PCOS patients have a higher risk of breast cancer[18].

In one study, unopposed estrogen has been shown to increase the level of IGF-1[25]. However, in another study, no relationship was found between the IGF-1 level and the risk of developing breast cancer[26].

Contrary to these studies, there are also results in various meta-analyses. Barry et al. suggested that patients with PCOS do not have an increased risk for breast cancer[16].

In other meta-analyses in the literature, they stated that the relationship between breast cancer risk and PCOS is complex and a clear conclusion could not be reached[17,19].

Eslami et al. compared the BIRADS scores reflecting breast densities of the normal group with those of the PCOS group and found no significant difference in breast density between the two groups[27].

When the ACR breast density category and BI-RADS score were compared, no statistically significant difference was found between the two groups (p=0.319 and 0.650, respectively). Contrary to the hypothesis we thought at the beginning of the study, we did not detect a significant difference in BI-RADS scores and breast density in PCOS patients compared with normoovulatory women. As in many studies in the literature, it can be said that the reason why this relationship has not been clarified is that PCOS has an environment of both unopposed estrogen and hyperandrogenemia. D'Amelio et al. showed a significant association between PCOS and benign breast pathologies[28]. In another study, they suggested that there was no significant association between benign breast pathologies and PCOS[29].

In our study, we did not find a significant difference between the two groups in terms of benign breast pathologies detected on ultrasound.

PCOS is divided into phenotypes. The clinical picture of hyperandrogenism varies in different PCOS phenotypes[30]. Metabolic disorder is also seen in PCOS patients, and it may affect the breast tissue[31]. However, as laboratory hyperandrogenism and metabolic status were not evaluated in our study and PCOS patients were not examined according to phenotypes, no comment could be made on metabolic status in PCOS, PCOS phenotypes, and breast density.

The limitation of our study is that this is a retrospective study. The advantageous aspect of our study is that age, BMI, gravida, and parity numbers were homogeneous for both groups.

Our study aimed to investigate the relationship between PCOS and breast density as well as breast cancer risk. Despite the existing epidemiological and experimental data suggesting a potential link between unopposed estrogen exposure and breast cancer development, there is no consensus in the literature regarding the association between PCOS and breast cancer risk. Our study utilized ACR breast density evaluation and BI-RADS scoring in mammography, which are considered reliable methods for assessing breast cancer risk. We found no significant difference in breast density and BI-RADS scores between the group of women with PCOS and the normoovulatory group. It is worth noting that the complex hormonal milieu of PCOS, characterized by both unopposed estrogen and hyperandrogenemia, may contribute to the lack of clarity in this relationship. Furthermore, our study did not reveal a significant difference in the incidence of benign breast pathologies between the two groups.

CONCLUSION

Our study did not provide evidence supporting an association between PCOS, breast density, and breast cancer risk as assessed by ACR breast density and BI-RADS scoring. Further research, including prospective studies with larger sample sizes and longer follow-up periods, is needed to elucidate the complex relationship between PCOS and breast cancer risk.

AUTHORS' CONTRIBUTIONS

ARŞ: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. **SAA:** Data curation, Investigation. **Eİ:** Data curation, Methodology. **İK:** Formal Analysis, Methodology, Writing – review & editing. **EK:** Formal Analysis, Validation. **DCÖ:** Project administration, Resources, Supervision, Visualization.

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ORIGINAL ARTICLE

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Tumor budding in invasive breast carcinoma: correlation with clinicopathological parameters, hormone receptor status, and survival: an observational study

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SUMMARY

OBJECTIVE: Tumor budding is currently thought to be associated with worse prognosis. This study aims to examine tumor budding in invasive ductal-type breast carcinoma and its relationship with other clinicopathological parameters and overall survival.

METHODS: All the H&E slides of 198 patients were re-evaluated for the histological grade, angiolymphatic invasion, perineural invasion, lymph node status, extranodal extension, multicentricity, pT, presence of the tumor budding, tumor budding score (i.e., low, intermediate, or high). Overall survival was considered the period after surgery until death. SPSS was used for statistical analysis.

RESULTS: Tumor budding was identified in 98 (49.5%) patients. Tumor budding score was low in 41 (41.8%) of 98 cases, intermediate in 25 (25.5%), and high in 32 (32.7%). We determined a strong correlation between tumor budding and poor prognostic variables such as tumor size, pT stage, angiolymphatic invasion, perineural invasion, number of metastatic axillary lymph nodes, overall survival, and extranodal tumor extension in metastatic lymph nodes. This strong correlation was also present for the tumor budding score.

CONCLUSION: Tumor budding may be a prognostic indicator for breast cancer.

KEYWORDS: Breast cancer. Breast tumor. Carcinoma, invasive ductal, breast. Survival.

INTRODUCTION

Breast cancers are the most common cause of mortality in women worldwide[1]. They are heterogeneous and have variable morphological and biological features and thus clinical behavior and therapeutic outcome. The histopathological assessment aims to provide an accurate diagnosis of the disease and prediction of tumor behavior to facilitate clinical and oncologic decision-making. Invasive ductal carcinoma constitutes the majority and is the cause of a great clinical burden[2]. In spite of the availability of treatment protocols, relapse and metastasis are known to occur. Therefore, additional and more efficient prognostic markers are required to predict prognosis and survival and also for individual treatment approaches[3-5].

Tumor budding (TB), which has previously been reported to predict survival in several solid organ tumors, is currently thought to be associated with worse prognosis[6,7].

TB is defined as the formation of single malignant cells or cell clusters of fewer than five malignant cells at the invasive tumor front and is associated with tumor invasion and distant metastasis[4]. The 2019 World Health Organization classification of colorectal cancer introduces TB as a second major grading criterion[8]. Studies reported that TB is also a novel prognostic indicator independent of tumor stage and grade in esophageal, gastric, ürinary bladder, and pancreatic tumors[9,10]. In invasive ductal carcinoma, a high number of tumor buds are associated with angiolymphatic invasion (LVI), lymph node metastasis, and shorter survival[11]. Extranodal extension (ENE) is defined as tumor cells penetrating through the capsule of a lymph node into the perinodal tissue. The importance of ENE in axillary lymph nodes in breast carcinoma was first reported in a series between 1936 and 1941[12]. From that day on, lots of studies conducted about this phenomenon and ENE has been found in association with worse prognosis in breast carcinoma. While we were doing this study, there was no study in the literature investigating the relationship between TB and ENE.

Therefore, this study aims to examine TB in invasive ductal-type breast carcinoma, and its relationship with other clinicopathological parameters, especially hormone receptor status, LVI, perineural invasion (PNI), metastatic lymph node status, ENE, and overall survival.

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METHODS

Study design and case selection

From June 2014 to January 2022, patients who had undergone breast carcinoma surgery at the Bolu Abant Izzet Baysal Training and Research Hospital were retrospectively scanned from the electronic database in the present observational study. Among them, some cases were excluded for any of the following criteria: (1) those whose diagnosis was not invasive ductal carcinoma, (2) those whose H&E-stained slides were not reached or available for review, (3) those who received neoadjuvant chemotherapy or radiotherapy, (4) those who died due to post-operative complications in the first month after surgery, and (5) those whose clinical data not to be reached. A total of 198 patients were included in the study.

Clinicopathological information, which included age, tumor size (TS), stage, and nodal status, was retrieved from pathological reports. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index analysis were retrieved from immunohistochemistry reports and slides were re-evaluated.

All cases were divided into molecular subtypes (i.e., Luminal A, Luminal B, HER2, and Triple-negative) according to the ER, PR, HER2, and Ki-67 immunohistochemical staining patterns. Overall survival was considered the period after surgery until the death of the patient. Death records were completed on August 2022.

All the H&E slides were re-evaluated for the histological grade (Modified Bloom-Richardson), LVI, PNI, lymph node status, ENE, multicentricity, pT, presence of the TB, and tumor budding score (TBS). TB was considered single tumor cells or cell clusters of up to four cells in the peripheral advancing tumor front, as indicated by ITBCC 2016. First, the cases were grouped as "tumor budding absent (TBA)" or "tumor budding present (TBP)." Then, TBS was evaluated with a three-tier score; low (0–4 buds), intermediate (5–9 buds), and high (10 or more buds) as also defined in ITBCC. TB was assessed by selecting a "hotspot area" chosen after a review of all available slides. The total number of buds was reported in an area measuring 0.950 mm^2, which corresponds to 20′ field in the Olympus CX43 microscope (Figure 1). We grouped lymph nodes into three groups as follows: negative, positive without ENE, and positive with ENE. ENE length was not measured in ENE-positive lymph nodes.

Ethical approval

The study was approved by the Clinical Researches Ethics Committee of the Bolu Abant Izzet Baysal University (Decision number: 164/2022).

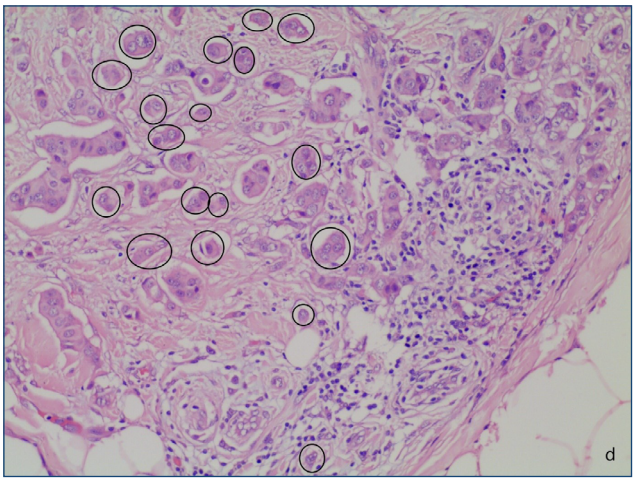

Figure 1. Tumor budding at the invasive front of invasive ductal carcinoma (H&E 200×). High tumor budding.

Statistical analysis

SPSS 15.0 for Windows was used for statistical analysis. Kolmogorov-Smirnov test was applied to the study variables for normality analysis. The variables with normal distribution were compared with the independent-samples t-test between two groups and with the one-way ANOVA test for three or more groups. These variables were expressed as mean±SD. Variables without normal distribution were compared by the Mann-Whitney U test in two groups and by the Kruskall-Wallis test in three or more groups. These variables were expressed as median (min–max). The comparison of categorical variables was conducted with the chi-square test. These variables were expressed as numbers and percentages. Pearson's correlation analysis test was used to observe the correlation between study variables. The sensitivity and specificity of study variables in determining TB were analyzed using receiver operative characteristics curve analysis. Kaplan-Meier analysis was used in the survey analysis of study variables. Statistical significance was accepted as $p<0.05$.

RESULTS

In this study, 198 samples of invasive ductal carcinoma were assessed. TB was identified in 98 (49.5%) patients and not identified in 100 (50.5%). TBS was low in 41 (41.8%) of 98 cases, intermediate in 25 (25.5%), and high in 32 (32.7%).

The average TS of the TBA and TBP groups was 19.5 mm (2–70 mm) and 25 mm (8–170 mm), respectively, and it was statistically significant ($p<0.001$). The median value of TS is 20 (8–105) mm in patients with low TBS, 25 (12–52) mm in patients with moderate TBS, and 40 (12–170) mm in patients with high TBS. TS significantly increased as the TBS increased ($p=0.001$).

A total of 51 patients were evaluated as pT1, 43 patients as pT2, 5 patients as pT3, and 1 patient as pT4 in the TBA group. A total of 24 patients were evaluated as pT1, 56 patients as pT2, 13 patients as pT3, and 5 patients as pT4 in the TBP group. It was statistically significant that patients with TB were in the advanced pT stage (p=0.002). TB was detected in 62 (72.9%) of 85 cases with LVI and 29 (76.3%) of 38 cases with PNI. Both were significant (p<0.001 and p<0.001) (Table 1).

In addition, the relationship of TBS with LVI and PNI was statistically significant (p=0.004 and p=0.01, respectively). The number of metastatic lymph nodes was between 0 and 51, and the average metastatic lymph node number was 4. The median value of the metastatic axillary lymph node in the TBA group was 0 (0–51) and in the TBP group was 2 (0–36), and this was statistically significant (p<0.001). As well as the TBS increased, metastatic lymph node count increased statistically (p<0.001).

ENE was detected in 35 patients (35.7%) in the TBP group and was detected in 14 patients (14%) in the TBA group. There was a significant correlation between TB and ENE (p<0.001). The rates of presence of ENE in the TBS groups were as follows: 6 cases (17%) in the low, 8 cases (23%) in the intermediate, and 21 cases (60%) in the high group. As the TBS increased, the presence of ENE increased statistically (p<0.001).

The mean follow-up period of the patients was 39.6 months, and the follow-up interval ranged from 3 to 97 months. The relationship between TB and cumulative survival was significant; 22 (22.4%) of the patients with TB died, and 76 (77.6%) were still alive (p=0.002). The median survival time was 43 (5–97) months in the TBA group and 27 (3–97) months in the TBP group (p=0.001) (Figure 2). In the overall survival analysis, mean survival times were significantly lower in the TBP group and TBS was also high (p<0.001 and p=0.004). The association of TB with age, molecular subtypes, multicentricity, and histological grade was not significant.

DISCUSSION

Invasive ductal carcinomas are heterogeneous and have variable morphological and biological features and thus clinical

Table 1. Tumor budding and clinicopathological parameters.

		Tumor budding present	Tumor budding absent	p-Value
Patients, n (%)		98 (49.5)	100 (50.5)	
Age (years)		55.9 (±13.2)	56.5 (±11.7)	0.20
Tumor size (mm, min–max)		25 (8–170)	19.5 (2–70)	<0.001
Molecular subtype (n)	Luminal A	33	49	0.08
	Luminal B	46	33	
	HER2	15	11	
	Triple Negative	4	7	
Histological grade, n (%)	Grade 1	22 (9.1)	33 (16.7)	0.053
	Grade 2	50 (25.3)	45 (22.7)	
	Grade 3	30 (15.2)	22 (11.1)	
Multicentricity, n (%)		13 (13.3)	10 (10)	0.47
pT stage (n)	pT1	24	51	0.002
	pT2	56	43	
	pT3	13	5	
	pT4	5	1	
Angiolymphatic invasion, n (%)		62 (72.9)	23 (27.1)	<0.001
Perineural invasion, n (%)		29 (76.3)	9 (23.7)	<0.001
Metastatic lymph node, n (min–max)		2 (0–36)	0 (0–51)	<0.001
Extranodal extension, n (%)		35 (35.7%)	14 (14%)	<0.001
Cumulative survival, n (%)	Alive	76 (77.6)	93 (93)	0.002
	Dead	22 (22.4)	7 (7)	
Survival time (month)		27 (3–97)	43 (5–97)	0.001

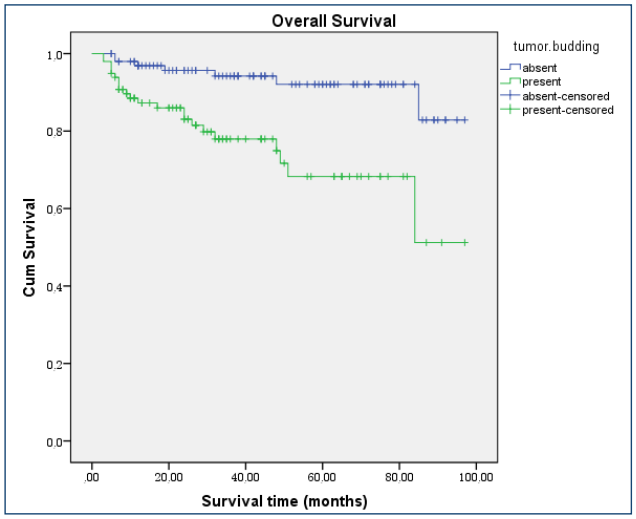

Figure 2. Kaplan-Meier overall survival curve for tumor budding.

behavior and therapeutic outcome. Therefore, additional and more efficient prognostic markers are required to predict prognosis and survival and also for individual treatment approaches[3-5]. TB is a histological process, which was described in colorectal carcinoma first by Imai in 1954[7]. In the ensuing years, it has been studied in many solid organ malignancies as a prognostic marker[4,13,14]. Therefore TB is advocated as a more sensitive prognostic factor, a predictor of aggressiveness and a worse outcome[4,6,15].

At the ITBCC, the method of evaluating, scoring, and reporting TB was standardized and detailed in colorectal carcinomas[7]. For other organ malignancies, this is still a subject of debate. So far, different studies have utilized different methods for the assessment of TB[16]. Most of them assessed TB in the low-high bud group with different cutoff values[4,17]. In spite of various evaluation methods, all these studies showed that high TBS was associated with poor prognosis and decreased survival[6,8,17]. In our study, TB was assessed by selecting a "hotspot area" measuring 0.950 mm^2 and scoring TB counts with a three-tier scoring system, as defined in ITBCC. Some studies used immunohistochemistry for evaluating buds, and some of them did not[4,11,18,19]. We did not perform immunohistochemistry as recommended at ITBCC.

In this study, TB was statistically associated with TS, pT stage, LVI, PNI, number of metastatic axillary lymph nodes, ENE, and overall survival. However, TB was not associated with age, molecular subtype, histological grade, and multicentricity. Previous studies investigated the association of hormone receptor status with TB. Some of them have found significant relationship with ER positivity[17,19], but Okcu et al. have not[4]. Similar to our study, Masilamani et al. evaluated the association between molecular subtype groups and have not found a significant association[20].

Therefore, many previous studies have found similar associations between TB and LVI, pT, and axillary lymph node metastasis[4,6,8,15,17-20]. In line with them, we found a significant association. Also in our TBS groups, as TBS increased, LVI and metastatic axillary lymph nodes increased.

Only a few studies focused on the association of PNI with TBS. While Okcu et al. found no relationship[4], we found a strong association between them. As TBS increases, PNI will also increase, which is a new contribution to the literature.

While we performed our study, there was no study that assessed the association between ENE and TB. In our study, there was a significant correlation between TB and ENE ($p<0.001$). In addition, as the TBS increased, the presence of ENE increased statistically ($p<0.001$).

Various studies investigated the association of TB with survival. Survival is evaluated as overall or cancer-specific. They have found a strong relationship, especially high TB groups have had lower survival times[4,6,8,17]. Li et al. have found that TB was an independent prognostic factor of cancer-specific survival[6]. In line with the literature, we found a significant relationship between TB and overall survival. Survival time was reduced in patients with TB, and as the TBS increased, survival time decreased.

Other methods are also useful in breast carcinoma survival. Preoperative magnetic resonance image has beneficial effects on survival rates of breast cancer patients[21]. Moreover, extracapsular extension in sentinel lymph node biopsy is also considered a predictor of survival[22]. Similarly, we found that TB was associated with survival in breast cancer cases.

Retrospective design and single-center nature of the study are limitations of this study. Yet, the strength is being the first study in the literature that reported the association between TB and breast cancer.

CONCLUSION

This study provides an extensive assessment of TB, and there is a strong correlation between TB and poor prognostic variables such as TS, pT stage, LVI, PNI, lymph node metastasis, overall survival, and ENE, which has not been the subject of the previous studies. This strong correlation was also present for the TBS. Based on all these results of this study, we can say that TB is a prognostic indicator, and the assesment of TB utilizing routine pathological slides is relatively easy and it does not bring additional cost. However, it needs standardization for evaluation and scoring.

ETHICS STATEMENT

This study has been approved by the directorate of the institution under decision number 164/2022.

AUTHORS' CONTRIBUTIONS

SPO: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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The relationship between serum leptin, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 levels and clinical parameters in primary fibromyalgia patients

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the levels of leptin, growth hormone, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 and their relations with clinical parameters in patients with primary fibromyalgia and healthy controls.

METHODS: Our study was performed on 30 female patients with primary fibromyalgia and 30 healthy controls. The levels of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 were measured by a two-site immunoradiometric assay. The serum level of leptin was measured by the ELISA kit.

RESULTS: The serum level of leptin was significantly higher, but the serum levels of insulin-like growth factor-1 were significantly lower in patients with fibromyalgia syndrome than healthy controls ($p<0.001$). The leptin level was positively correlated with the Visual Analog Scale, Fibromyalgia Impact Questionnaire score, Beck Depression Inventory score, tender point count, age, and duration of disease ($p<0.001$), but it was negatively correlated with insulin-like growth factor-1 ($p<0.001$). The insulin-like growth factor-1 level was negatively correlated with age, Visual Analog Scale, Fibromyalgia Impact Questionnaire and Beck Depression Inventory scores, duration of disease, and tender point count ($p<0.001$).

CONCLUSION: Our results indicate that high levels of serum leptin and low levels of serum insulin-like growth factor-1 may play a role in the physiopathogenesis of fibromyalgia and may be related to some symptoms.

KEYWORDS: Fibromyalgia. Leptin. Growth hormone. IGF-1. IGFBP-3.

INTRODUCTION

Primary fibromyalgia syndrome (FMS) is considered a multifactorial disorder characterized by widespread musculoskeletal pain, diffuse tenderness, psychological distress, fatigue, and sleep disturbances. Although several mechanisms are suggested, the etiology and pathophysiology of fibromyalgia have not yet been understood completely. Sleep disorders, changes in muscle oxygenation, and psychological, biochemical, hormonal, and immunological factors are suggested to be effective in the etiopathogenesis of FMS[1-3]. It is demonstrated that FMS symptoms are originated from the interaction between the autonomic nervous system, hypothalamus-pituitary-adrenal axis, and immune system. It was indicated that insulin-like growth factor (IGF-1) and growth hormone (GH) levels are low and this is a negative factor for skeletal muscle homeostasis. In experimental studies, it was shown that GH administration to fibromyalgia patients with low IGF-1 levels provides an improvement in FMS symptoms. IGF-1 has an anabolic effect and is the major mediator for GH needed in muscle homeostasis. In most studies, the level of serum IGF-1 is generally measured instead of GH because its half-life is very short. IGF-1 level is an indicator of GH secretion. Symptoms such as lack of energy seen in deficiency of GH in adults, poor general health, reduced exercise capacity, muscle weakness, cold intolerance, and impaired cognitive functions are similar to the symptoms described in FMS patients[4-8]. It is stated that the levels of leptin and growth factors (IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3)) vary in patients with fibromyalgia and this is a negative factor for homeostasis of the hypothalamic-pituitary-adrenal axis and skeletal muscle[5]. Leptin is in close interaction with HPA, thyroid, and GH axes. Both the sympathetic nervous system and the HPA axis regulate the secretion of leptin and are stress-activated. Leptin secretion is inhibited by the sympathetic nervous system while activated by the HPA system[8,9]. In recent years, the possible role of leptin in the etiology and pathogenesis of

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fibromyalgia has been suggested in some studies, but the results are conflicting[6-14]. Finding out the causes of symptoms can play a key role in the treatment of fibromyalgia. This study was planned to evaluate the relationship between FMS and leptin, a hormone that has a wide range of physiological effects, and GH, IGF-1, and IGFBP-3, which have important roles in different processes in organisms with clinical parameters.

METHODS

A total of 30 fibromyalgia patients, applied to Physical Medicine and Rehabilitation Outpatient Clinics of Dicle University Faculty of Medicine, having complaints of pain and fatigue, lasting for at least 3 months, existing 11 painful of 18 tender points, and aged between 25 and 55 years were included in the study, and 30 healthy females with similar age were included for the control group. These patients were examined by a rheumatologist to confirm or to exclude the FMS diagnosis according to the 1990 classification criteria of the American College of Rheumatology[15]. All individuals were assessed for clinical findings. Beck Depression Inventory (BDI) score for depression, Fibromyalgia Impact Questionnaire score (FIQ) for functional disability, Visual Analog Scale (VAS) for intensity of pain, and tender point count were evaluated. A standard form was fulfilled, evaluating whether there were complaints accompanied or not for both groups. Exclusion criteria were as follows: a recent or history of a defined systemic, metabolic, endocrine, tumoral, infectious, neurological, or cardiovascular disease, pregnancy, any drug or alcohol addict, those who have pain and limitation of movement in their lower extremity joints, and any medical treatment except for analgesics within the last month. The Human Studies Research Committee of the University of Dicle approved all procedures, and written informed consent was obtained from each subject before inclusion in the study.

Complete blood count, routine biochemical tests (i.e., serum glucose, insulin, urea, creatinine, uric acid, calcium, P, ALP, ALT, AST, LDH, CK, and GGT), erythrocyte sedimentation rate, C-reactive protein, PTH, GH, and thyroid function tests were performed. After 12 h of the hunger period, 5 mL of antecubital venous blood samples were taken from all subjects, and their sera were separated with centrifugation under 37°C for 5 min at 4,000 rpm. Separated sera were kept at -70°C until study. Within the working day, all sera were dissolved, and parameters were studied on the same day and at one time in the calibrated test machines.

The levels of IGF-1 and IGFBP-3 were measured by a two-site immunoradiometric assay (Diagnostic Systems Laboratories, Inc., TX, USA). For IGF-1, the sensitivity was 0.8 ng/mL, and intra-assay and inter-assay coefficients of variation were 3.8 and 4.9%, respectively. For IGFBP-3, the sensitivity was 0.8 ng/mL, and the intra-assay and inter-assay coefficients of variation were 5.6 and 7.1%, respectively. The assays were analyzed in duplicate. The level of leptin was measured by the ELISA kit (Cayman Chemicals, USA). The detection limit was 0.5 ng/mL. The intra-assay coefficients of variation were 6.0% (n=8) at 7.6 ng/mL and 2–3% (n=8) at 20.12 ng/mL. Serum insulin was measured by the electro-chemiluminescence immunoassay analyzers (Roche Elecsys-1010 and Modular Analytics E-170 Indianapolis, USA). The minimum detection limit was 0.2 µg/mL, and the intra-assay coefficient of variation was 4.9%. Common biochemical parameters were determined by standard laboratory methods.

Statistical analysis

SPSS 25.0 for the Windows program was used to perform statistical analysis. Definitive tests were applied to the data, and the mean value and standard deviation were found. The Kolmogorov-Smirnov distribution test was used for the examination of normal dispersion. Within two groups state, related to the comparison of quantitative data, independent-sample test and Mann-Whitney U test were used in the comparison of groups. Pearson correlation analysis was used within the cases showing normal distribution in the comparison of two quantitative data. Results were evaluated two-way, with 95% confidence interval and $p<0.05$ significance level.

RESULTS

The demographic, clinical, and biochemical characteristics of fibromyalgia and control groups are given in Table 1.

The levels of serum leptin, tender point score, VAS, FIQ score, and BDI score were significantly increased in women with FMS than in healthy women ($p<0.01$). Serum IGF-1 and GH levels were significantly lower in women with FMS than in healthy women ($p<0.01$). Fasting blood glucose, insulin, and IGFBP-3 were not found significantly different between healthy subjects and women with FMS ($p>0.05$).

In women with FMS, serum leptin level was positively correlated with VAS score ($r=0.643$; $p<0.001$), FIQ score ($r=0.681$; $p<0.001$), tender point score ($r=0.674$; $p<0.001$), age ($r=0.760$; $p<0.001$), BDI score ($r=0.783$;$p<0.001$), and duration of disease ($r=0.755$; $p<0.001$), and leptin level was negatively correlated with IGF-1 ($r=-0.648$; $p<0.001$) and GH ($r=-0.820$ $p<0.001$) (Figures 1 and 2). The IGF-1 level was negatively correlated with age ($r=-0.665$; $p<0.001$), VAS score ($r=-0.718$; $p<0.001$), FIQ score ($r=-0.545$; $p<0.001$), tender point count ($r=-0.460$;

Table 1. Demographic and clinical characteristics and biochemical parameters of the fibromyalgia and control groups.

	Fibromyalgia group (n=30)		Control group (n=30)		p
	Mean	SD	Mean	SD	
Age (years)	37.90	9.37	38.23	8.76	0.784
BMI (kg/m²)	25.81	1.98	25.74	1.93	0.824
Duration of disease (years)	3.06	1.51	–	–	–
Tender point count	14.12	2.46	1.93	0.67	<0.001
VAS (pain intensity)	5.85	1.26	2.57	1.09	<0.001
FIQ score	58.19	9.53	–	–	–
BDI score	12.31	4.02	3.55	1.90	<0.001
Glucose (mg/dL)	92.07	10.51	91.57	9.81	0.850
Insulin (μU/mL)	7.56	2.83	7.27	2.79	0.700
GH (ng/mL)	0.31	0.14	1.61	0.91	<0.001
Leptin (ng/mL)	36.34	10.04	16.18	7.40	<0.001
IGF-1 (ng/mL)	158.23	13.83	243.84	83.87	<0.001
IGFBP-3 (ng/mL)	2561.64	597.37	2539.00	605.24	0.885

VAS: Visual Analog Scale; FIQ: Fibromyalgia Impact Questionnaire; BDI: Beck Depression Inventory; GH: growth hormone; IGF-1: insulin-like growth factor; IGFBP-3: insulin-like growth factor binding protein-3.

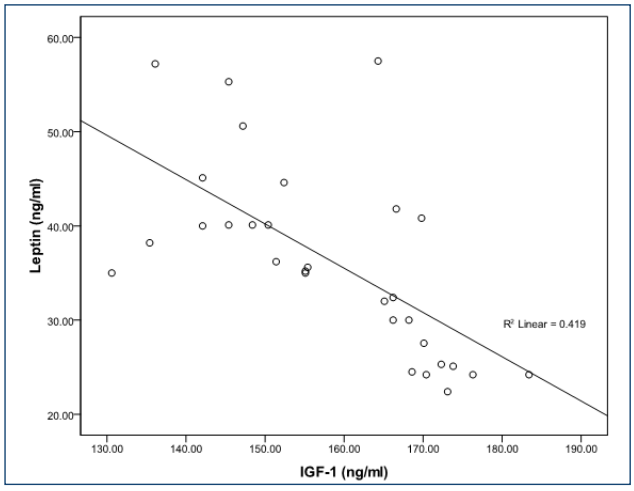

Figure 1. The correlations between leptin and the levels of insulin-like growth factor-1.

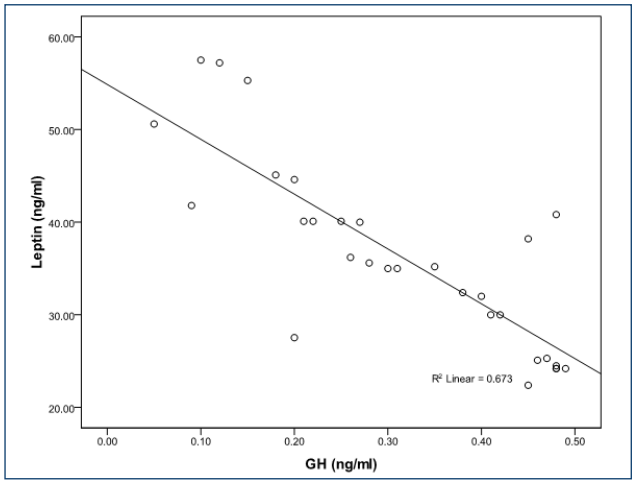

Figure 2. The correlations between leptin and the levels of growth hormone.

p<0.001), BDI score (r=-0.543; p<0.001), and duration of disease (r=-0.798; p<0.001) (Figure 2). We found no association between glucose, insulin, and IGFBP-3 or other parameters in either subjects with fibromyalgia.

DISCUSSION

The etiology and pathogenesis of fibromyalgia have not been fully explained[1-3]. In our study, we measured serum leptin, IGF-1, and IGFBP-3 levels in patients with FMS and evaluated their relationship with clinical parameters. The results of the studies which show that changes in serum IGF-1 levels play a role in FMS physiopathogenesis are inconsistent[5,6,9,12,15-20].

In their study on 47 patients with fibromyalgia and 28 healthy women, Tander et al.[5] found that GH and IGF-1 and IGFBP-3 levels were not significantly different from controls, but serum ghrelin levels were lower. In a study, McCall et al.[19] found the level of IGF-1 similar to those of the healthy control group; hence, with an increase in age and obesity, IGF-1 levels decrease. Also, Bjersing et al.[21] found that serum IGF-1 and IGFB3 levels remained same during 15 weeks of aerobic exercise in FMS patients. However, Bennett et al.[16] found that circulating IGF-1 and GH were low in patients compared with the control group. Atalay et al.[15] also found that low serum IGF-1 levels were associated with the number of tender points, muscle spasm, and stiffness in female patients with FMS.

Lack of GH secretion may also cause muscle microtrauma and/or distortion in the recovery of microtrauma in normal processes in patients at the same time. Many FMS patients have low serum GH levels, with a hypothesized etiology of dysregulated GH/IGF-I axis and in the sympathetic stress axis

as well[17,18]. In another study, they were reported that the pituitary function was normal in fibromyalgia and the changes in the hypothalamus-GH-IGF-1 axis were largely due to hypothalamic origin and that GH cure should be recommended accordingly in future studies[20].

Serum IGF-1 and GH levels in women with FMS were lower than in healthy women in our study compatible with the literature[15,16]. Consistent with the literature, IGFBP-3 levels in FMS were not different from the control group[5,21].

Both hypothalamo-pituitary-IGF-1 axis and leptin levels may be altered in FMS due to increased somatostatin tone[5,19]. Ataoglu et al.[10] found the serum leptin level to be significantly higher in patients compared with the healthy group, but they could not find a significant relationship between leptin level and clinical and inflammatory parameters. On the other hand, another study found levels of serum leptin significantly higher in fibromyalgia patients[13]. In this study, it was recommended that the interaction of leptin and the HPA could play a role in FMS etiopathogenesis and further studies on leptin had to be done. Koca et al.[7] found that leptin (high), GH (low), and IGF-1 (low) levels in the FMS group were independent of disease severity but were statistically different and correlated with BMI. They suggested that these findings may be related to hypothalamo-pituitary axis dysfunction, BMI, and energy metabolism[22].

In our study, we found out that serum leptin levels are high in FMS patients than those of healthy controls, while IGF-1 and GH are low; leptin levels were negatively correlated with IGF-1 and GH significantly. Increased leptin levels may play a role in the severity of fibromyalgia. Our results showed compatibility with the studies showing that there was an important relationship between high levels of leptin, low levels of IGF-1, and primary FMS. A decrease in IGF-1 and GH levels seems to be associated with pain scores. The duration of illness in the FMS group was similar to the literature. These findings about FMS associated with pain and depression are consistent with previous studies[23].

In light of our study and literature, we can say that many of the clinical features of FMS may be related to neuroendocrine or metabolic events, that the levels of GH and IGF-1 in FMS are lower than in healthy controls, and that there is a deficiency in GH secretion. The greatest advantage of our study is that it is the first study analyzing the relationship between leptin levels based on clinical data such as BDI, VAS, and FIQ scores in addition to HPA axis hormones such as GH and IGF-1 in FMS patients. On the contrary, the subjective evaluation of clinical findings and the absence of an assessment tool such as an algometer are the shortcomings of our study. Besides, our study will be a good guide for studies to find the relationship between clinical parameters such as VAS, BDI, and FIQ scores, and leptin-IGF-1-GH axle.

AUTHORS' CONTRIBUTIONS

YA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization. Supervision, Writing – original draft. **TŞ:** Software, Formal Analysis, Validation Supervision, Visualization, Writing – review & editing. **HKA:** Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **SS:** Conceptualization, Data curation, Investigation, Resources, Validation, Visualization.

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ORIGINAL ARTICLE

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Investigation of the effectiveness of teledermatology in the diagnosis of skin lesions in pediatric patients

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SUMMARY

OBJECTIVE: Teledermatology is the use of communications technology to enable the remote evaluation of skin lesions. Dermatological complaints are common among pediatric patients and should be handled differently than adults. The aim of this study is to group the dermatological lesions of pediatric patients who visited a dermatology outpatient clinic and to investigate in which groups the teledermatology method is more effective.

METHODS: This is a prospective observational study. Images of skin lesions, which were examined face-to-face in a dermatology outpatient clinic, were transmitted to another dermatologist via telecommunication. The diagnoses by the physician who examined patients face-to-face were compared with the diagnoses by the teledermatologist. Informed consent was obtained from the parents or legal representatives of all patients participating in this study.

RESULTS: A total of 93 pediatric patients were evaluated. In our study, the diagnoses by a dermatologist who evaluated patients face-to-face and the diagnoses by a teledermatologist were in agreement with 74.2% of the time. There was 100% agreement between both dermatologists for the diagnosis of acne and scabies. The diagnosis for verruca was consistent with 91.7% of the time, and for atopic dermatitis, it was 72.7%. There was a 25% consistency between both dermatologists on the diagnosis of contact dermatitis. The diagnostic consistency between both physicians was 53% in the erythematous disease group, 89% in the papulopustular group, and 70% in the pigmented group.

CONCLUSION: Teledermatology is a reliable diagnostic method that shortens the waiting time of patients and provides a quick consultation with a dermatologist. When using the teledermatology method, it is important to know which skin lesions or disease groups are more accurately diagnosed.

KEYWORDS: Skin disease. Pediatrics. Telemedicine. Diagnosis.

INTRODUCTION

Teledermatology is an alternative examination method that enables remote evaluation of skin lesions of patients using visual communication technologies[1]. Its use has been increasing in recent years. Therefore, studies are needed to confirm the clinical accuracy, safety, and efficacy of the teledermatology method. Dermatological complaints are common in pediatric patients, and approximately 10–30% of all patients admitted to the hospital have skin lesions[2]. Skin diseases seen in children should be handled differently than in adults. There are frequently encountered differences with children, such as diseases specific to the pediatric period, different side effects of treatments, and different treatment strategies. Long appointment times for examination and the need for the patient to apply to more than one department cause dissatisfaction of the patients and their relatives, as well as an increase in health expenses[3]. Effective use of teledermatology can be beneficial in such cases. In addition, due to this method, other physicians (pediatricians, emergency physicians, etc.) can obtain a dermatologist's opinion on skin lesions they are not familiar with[2,4,5]. As the body is not evaluated as a whole and palpation cannot be performed in teledermatology, more studies should be conducted to evaluate its effectiveness.

The aim of this study is to group the dermatological lesions of pediatric patients who applied to the dermatology outpatient clinic and to investigate in which groups the teledermatology method is more effective.

METHODS

Patients below 16 years of age who visited the dermatology department of the University Hospital between April 15, 2022 and November 1, 2022, were included in this prospective and observational study. Informed consent was obtained from the parents or legal representatives of all patients participating in this study. Those who refused to participate in the study and those who did not accept imaging of skin lesions were excluded from this study (Figure 1).

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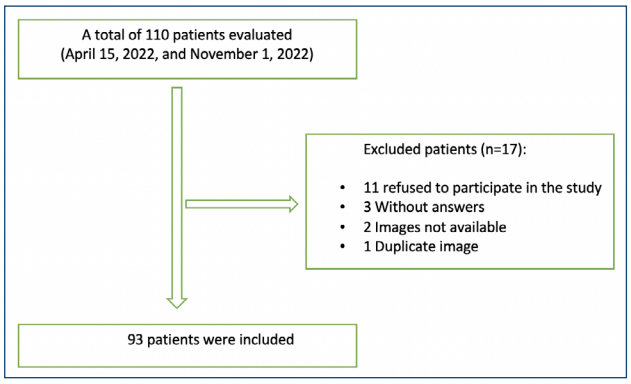

Figure 1. Patient flow chart.

Patients with visible skin lesions, high-resolution photographs, and previously undiagnosed conditions were included in this study. Images of the skin lesions of patients who were examined face-to-face in the dermatology outpatient clinic were transmitted to another dermatologist via telecommunication. The physicians were in different hospitals and did not see each other. A mobile phone with a 16-MP camera was used to photograph the lesions.

The photo shoot was standardized as much as possible, and a neutral background was preferred. Photographs of the lesion area were taken without the use of flash in a well-lit room using autofocus. The teledermatologist numbered each image, added the date and time, and recorded it on a prepared form. At the end of the day, both physicians compared the patients' diagnoses. In this way, the dermatological lesion group in which the teledermatology method was effective was determined. Since teledermatology is based on images, skin lesions were divided into four groups according to their appearance: erythematous, papulopustular, pigmented lesions, and hair diseases.

The approval number 2022-399 dated 10.01.2023 was obtained from the University Ethics Committee to allow the study to be conducted.

Statistics

The behavior of quantitative variables was expressed using centralization and measures of variance: mean±SD. Exact measuring (where the sample size is low) and chi-square tests were used to identify differences in ratios or relationships between categorical variables. To show the behavioral differences of the group, the Mann–Whitney U-test method was used. Statistical significance was determined as p=0.05 for all cases. Statistical analyses were provided with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, NY, IBM Corp.) software program.

RESULTS

A total of 93 patients were evaluated, of whom 52 (55.9%) were females and 41 (44.1%) were males. The mean age was 11.03±4.62. There were 24 diagnosed diseases after the face-to-face examinations. The most common diagnoses were acne vulgaris in 14 (15.1%), verruca in 12 (12.9%), scabies in 11 (11.8%), and atopic dermatitis in 11 (11.8%). Among the disease groups, there were 34 patients (36.6%) in the erythematous group, 45 (48.4%) in the papulopustular group, 10 (10.8%) in the pigmented group, and 4 (4.3%) with hair diseases. When evaluated in terms of the duration of the disease, 26 (28%) patients were evaluated as acute and 67 (72%) patients as chronic. The diagnoses by the dermatologist who evaluated the patients face-to-face and through teledermatology were consistent 74.2% of the time. Diagnoses and demographic information of the patients are shown in Table 1.

There was 100% agreement between both dermatologists for diagnoses of acne and scabies. Verruca diagnosis was consistent 91.7% of the time, and atopic dermatitis 72.7%. However, there was only 25% agreement between both dermatologists on the diagnosis of contact dermatitis; and it was found to be statistically significant (p<0.001). The patients were divided into four groups (erythematous, papulopustular, pigmented, and hair diseases). The agreement between the diagnoses of both physicians was 53% in the erythematous disease group, 89% in the papulopustular group, and 70% in the pigmented group (p=0.001). Rates of correct diagnoses by the teledermatological method in the erythematous disease group were lower compared with other groups. The difference between the other groups was statistically significant (p=0.001). For papulopustular, the rate of teledermatologically correct diagnoses was higher in the disease group compared with the other groups (p=0.001).

DISCUSSION

In the field of dermatology, where visuality is important, teledermatology comes to the fore. Studies have shown that the teledermatology method has been used successfully during the COVID-19 pandemic[6-8]. These studies have generally been conducted among adult patients. There are very few studies investigating the effectiveness of pediatric teledermatology. In our study, there was 74.2% agreement between the diagnoses of the dermatologist who examined the patients face-to-face and the teledermatologist. In a study by Chen et al., the consistency among the physicians was 48%[9]. Heffner et al. reported this rate as 82%[10]. In another study conducted to investigate the effectiveness of the teledermatology method, there was an agreement of 78% among the diagnoses[11].

Table 1. Demographic and clinical characteristics.

		n (%)	Dermatologist diagnosis (Teledermatology)		p-value
			Diagnostic Agreement		
			Yes 69 (74.2)	No 24 (25.8)	
Age (mean±SD)	Year	11.03±4.62	11.22±4.51	10.5±4.98	0.566
Gender	Female	52 (55.9)	39 (75)	13 (25)	1.000
	Male	41 (44.1)	30 (73.2)	11 (26.8)	
Duration of the disease	Acute	26 (28)	16 (62)	10 (38)	0.141
	Chronic	67 (72)	53 (79)	14 (21)	
Disease group	Erythematous	34 (36.6)	18 (53)	16 (47)	0.001
	Papulopustular	45 (48.4)	40 (89)	5 (11)	
	Pigmented	10 (10.8)	7 (70)	3 (30)	
Dermatologist diagnosis (face-to-face)	Acne vulgaris	14 (15.1)	14 (100)	0 (0)	<0.001
	Verruca	12 (12.9)	11 (91.7)	1 (8.3)	
	Scabies	11 (11.8)	11 (100)	0 (0)	
	Contact dermatitis	8 (8.6)	2 (25)	6 (75)	
	Atopic dermatitis	11 (11.8)	8 (72.7)	3 (27.3)	

Acne vulgaris is a common skin disease. A total of 85–100% of people may encounter this disease at some point in their lives. Studies have shown that the diagnosis of acne is effectively diagnosed through teledermatology[12]. Similarly, in a study involving 2,459 patients using the teledermatology method, the diagnosis of acne was 99% accurate[13]. In our study, there was 100% agreement between the diagnoses of both physicians in all the acne patients. In a study, in which the treatment and follow-up of patients diagnosed with acne were conducted by teledermatology, patient satisfaction was found to be 92.3%[14]. Acne is a disease that needs to be diagnosed and treated quickly due to the scars and post-inflammatory hyperpigmentation it can leave on the skin. As it is not always possible for patients to reach dermatology outpatient clinics, it is considered safe to manage the diagnosis and treatment of patients by consulting a dermatologist via teledermatology in primary care.

Surprisingly, there was 100% consensus among physicians about the diagnosis of scabies. This may be due to good imaging of scabies-specific lesions and obtaining a good anamnesis from the patient. The use of teledermatology as an effective tool in diagnosing scabies is important. Thus, scabies patients can be diagnosed easily and quickly. Possible outbreaks can be prevented by isolating these people from crowded environments and raising awareness about the disease[15]. In one study, scabies marks and crusting were seen on the skin of a patient whose photographs were brought by family members. Afterward, the patient was successfully diagnosed for scabies[16].

Atopic dermatitis is an important global public health problem. These patients should be diagnosed early and followed up closely. In a study conducted by Giavina-Bianchi et al., the accuracy rate of diagnosis of atopic dermatitis via the teledermatology method was 84.4%[17]. In our study, the diagnosis of atopic dermatitis was the third most common diagnosis. In other studies, this diagnosis is the most common or the second most common diagnosis among pediatric patients[17,18]. It is important to use the teledermatology method in the diagnosis of atopic dermatitis because it is one of the most common diseases during the pediatric period. Using teledermatology is important because it eliminates the need for a face-to-face appointment with a dermatologist. In a study conducted by Mehrtens et al., they found that the teledermatology method provided approximately 40% of reduction in face-to-face examination appointments[19].

Diagnostic accuracy was low in cases of erythema, and this was consistent with similar studies in the literature[9]. In one study, teledermatological diagnostic agreement was found to be lower in such diseases as seborrheic dermatitis, pityriasis rosea, and xerosis with erythema and scaling compared with other diseases[20]. This may be because erythematous diseases have a wide list of differential diagnoses. In a study by Warshaw et al., the diagnostic agreement of pigmented lesions with the teledermatology method was found to be 81%[21]. In our study, even if 70% correct diagnosis was made with the teledermatology method in patients with pigmented skin

lesions, teledermatology should be used with caution, given the potential for malignancy of pigmented lesions.

This method can provide benefits in many respects, such as obtaining a dermatologist's opinion on patients in a short time frame and reducing waiting times and costs. Pediatricians frequently encounter patients with dermatological complaints and may have difficulties in diagnosing them. In one study investigating the dermatological diagnosis accuracy of pediatric patients, pediatricians made the correct diagnosis in only 76% of the patients[22]. Hence, it is important to contact a dermatologist at regular intervals. In another study, it was reported that the dermatology patients had a longest examination waiting period among all pediatric diseases, and teledermatology shortened this period significantly and served as a kind of triage[23]. Yet, in another study, the teledermatology method was shown to be very effective in the diagnosis of common skin lesions[24]. We believe that making more frequent and optimized use of teledermatology will be beneficial for public health. As research on teledermatology increases, effective areas of use can be determined, and guidelines and standards can be updated in this way.

Limitations

A non-diverse study population and a relatively small number of patients were the limitations.

CONCLUSION

Teledermatology is a reliable diagnostic method that shortens the waiting time of the patients and provides a quick consultation with the dermatologist. While using the teledermatology method, it is important to know the skin lesions or disease groups for which it is more effective. The teledermatology method may allow the dermatological evaluation of patients during quarantine periods, such as the COVID-19 pandemic, and natural disasters, including earthquakes.

HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1964 and its later amendments.

CONSENT

Informed consent was obtained from the parents or legal representatives of all patients participating in this study.

CONSENT FOR PUBLICATION

There are no details on individuals reported in the article. Consent for publication is not applicable in our study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The approval number 2022-399 dated 10.01.2023 was obtained from the Bezmialem Vakif University Ethics Committee to allow the study to be conducted.

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AUTHORS' CONTRIBUTIONS

NT: Conceptualization, Data curation, Formal Analysis, Funding acquisition Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **OSK:** Data curation, Formal Analysis, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Ultrasonography, macroscopy, and frozen section: which is better for predicting deep myometrial invasion in endometrial cancer?

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SUMMARY

OBJECTIVE: The aim of this study was to compare the power of preoperative transvaginal ultrasonography, intraoperative macroscopic examination, and frozen section for predicting deep myometrial invasion in endometrial cancer.

METHODS: This is a retrospective review involving 68 patients who underwent surgical staging for endometrial cancer from 2014 to 2017. Patients with grade 3 endometrial cancer and non-endometrioid tumors were excluded. The findings related to preoperative transvaginal ultrasonography, intraoperative macroscopic examination, and frozen section were compared with definitive histopathological diagnosis.

RESULTS: The mean age, gravidity, and body mass index of the patients were 58.1±8.9 years (range: 30–80 years), 3.2±2.1 (range: 0–9), and 33.5±6.6 kg/m^2 (range: 20–52 kg/m^2), respectively. Only 11 (16.2%) patients were in the premenopausal period, while 57 (83.8%) were in the postmenopausal period. Grade 1 endometrial cancer was found in 29 patients (42.6%) and grade 2 tumors were specified in 39 patients (57.4%). Stage IA disease was found in 45 (66.2%) patients, while stage IB disease was observed in 23 (33.8%) patients. The 5-year survival rate was 91.2%. The sensitivity of preoperative transvaginal ultrasonography, intraoperative macroscopic examination, and frozen section were 56, 34, and 52%, respectively, for predicting deep myometrial invasion. In contrast, the specificity of preoperative ultrasonography, intraoperative macroscopic examination, and frozen section were 86, 100, and 100%, respectively.

CONCLUSION: Transvaginal ultrasonography and intraoperative frozen section were found to have similar sensitivity and specificity for predicting deep myometrial invasion. Preoperative transvaginal ultrasonography appears as an efficient approach for predicting endometrial cancers with deep myometrial invasion.

KEYWORDS: Endometrial cancer. Myometrium. Prognosis. Survival.

INTRODUCTION

Endometrial cancer is the sixth most commonly diagnosed cancer and the 14th leading cause of cancer-related deaths in women worldwide[1]. It is recognized as the most common gynecological malignancy in the United States of America (USA), and the incidence of endometrial cancer in this country is significantly higher than that of other developed countries. The American Cancer Society has estimated that 61,880 new cases would be diagnosed and 12,550 women would die from endometrial cancer in the USA in 2022[2].

Endometrial cancer most commonly affects postmenopausal women. Studies have reported that 3–20% of women with postmenopausal bleeding have endometrial cancer, and endometrial hyperplasia is detected in 5–15% of them[3,4].

The most common type of endometrial cancer is endometrioid adenocarcinoma[5]. Myometrial invasion, lymphovascular space invasion, lymph node involvement, and recurrence have been designated as the most important prognostic factors for endometrial cancer[6]. Among these factors, myometrial invasion appears as an early indicator for the progression of disease, as it has been defined as the invasion of cancer cells into myometrium[7]. Studies have reported that myometrial invasion is associated with lymphovascular space invasion, lymph node involvement, recurrence, and survival of the patients with endometrial cancer. Hence, the depth of myometrial invasion is considered a critical component of surgical-pathological staging[8]. In 2021, the staging system for endometrial cancer has been updated by International Federation of Gynecology and Obstetrics (FIGO). According to this system, stage IA refers to tumors with myometrial invasion less than 50% and stage IB indicates tumors with at least or more than 50% of invasion into myometrium[8,9].

The aim of this study was to compare the power of preoperative transvaginal ultrasonography, intraoperative macroscopic examination, and frozen section for predicting deep myometrial invasion in endometrial cancer.

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METHODS

This is a retrospective review involving 68 patients who underwent surgical staging for endometrial cancer at the gynecological oncology department of Eskisehir Osmangazi University Hospital between 2014 and 2017. The study protocol was approved by the Institutional Review Board and Ethical Committee of Eskisehir Osmangazi University Medical Faculty (grant number: 45425468-32/ 21.08.2017). Written informed consent was obtained from all the participants.

A total of 349 patients were diagnosed with endometrial cancer histopathologically between 2014 and 2017. After excluding 281 patients with non-endometrioid endometrial cancer and/or grade 3 tumors, 68 patients were included for final analysis. Data related to age, gravidity, body mass index, presenting symptoms, menopause, stage, grade, and survival were derived from the patients' records. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Transvaginal ultrasonography was performed in the dorsal lithotomy position after ensuring that the patient's bladder was empty. The uterus was scanned thoroughly, in the longitudinal plane and in the transverse plane, from the cervix to the fundus. Deep myometrial invasion was identified as the infiltration of at least 50% of the myometrial thickness. The endometrial biopsy results were obtained from the sonographer.

All patients who had the histopathological diagnosis of endometrial cancer underwent total extrafascial hysterectomy, bilateral salpingooophorectomy, omental biopsy, and lymph node sampling. Peritoneal cytology was obtained from all patients upon entry into the peritoneal cavity. To specify deep myometrial invasion, the hysterectomy material was transversely cut into two sections and macroscopically examined under the supervision of other gynecological oncology experts and pathologists.

After macroscopic examination was completed, the hysterectomy material was sent to the pathology department for frozen section. The uterus was sliced transversely at 5 mm intervals and stained with hematoxylin and eosin so that the depth of myometrial invasion could be determined microscopically.

Patients with deep myometrial invasion, identified through preoperative transvaginal ultrasonography and/or intraoperative macroscopic examination or frozen section, underwent omentectomy, bilateral pelvic lymph node sampling, and paraaortic lymph node sampling. Staging was conducted based on FIGO criteria[9].

Collected data were analyzed by Statistical Package for Social Sciences version 21.0 (SPSS IBM, Armonk, New York, USA). Continuous variables were expressed as mean or mean±standard deviation (range: minimum-maximum), whereas categorical variables were denoted as numbers or percentages where appropriate. Mann-Whitney U test and chi-square test were used for the comparisons. Sensitivity and specificity values were computed by McNemar's test. Kaplan-Meier curves were drawn to show overall survival with respect to histology, stage, and body mass index. Two-tailed $p<0.05$ were accepted as statistically significant.

RESULTS

The mean age, gravidity, and body mass index of the patients were 58.1±8.9 years (range: 30–80 years), 3.2±2.1 (range: 0–9), and 33.5±6.6 kg/m^2 (range: 20–52 kg/m^2), respectively. The most common presenting symptom was postmenopausal bleeding, which was observed in 55 patients (80.9%). Among all patients, 11 (16.2%) were in the premenopausal period, while 57 (83.8%) were in the postmenopausal period. Grade 1 endometrial cancer was found in 29 patients (42.6%) and grade 2 tumors were specified in 39 patients (57.4%). Stage IA disease was found in 45 (66.2%) patients, while stage IB disease was observed in 23 (33.8%) patients. The overall survival rate was 91.2%. For stage 1a patients, the 5-year overall survival was 97.8%, whereas it was 78.3% for patients between stage 1b and stage 4b (p=0.008). BMI was calculated as weight in kilograms divided by height in meters squared, and participants were categorized into two groups, namely, non-obese (<30.0) and obese (≥30.0)[10], according to the World Health Organization classification. For the patients with BMI<30.0, the 5-year overall survival was 95.7% and for the patients with BMI≥30.0 it was 88.6% (p=0.362). Figure 1 demonstrates the overall survival rates with respect to body mass index and stage.

Table 1 shows the demographic and clinical characteristics of the patients with respect to the depth of myometrial invasion. The patients with myometrial invasion <50% and the patients with deep myometrial invasion were statistically similar in the aspects of age and body mass index. The number of premenopausal patients was significantly higher in patients with histopathologically confirmed myometrial invasion <50% (p=0.012). The number of patients predicted to have deep myometrial invasion by preoperative transvaginal ultrasonography, intraoperative macroscopy, and frozen section was significantly higher in patients with histopathologically confirmed deep myometrial invasion (p=0.001, p<0.001, and p<0.001, respectively). The overall survival rate was significantly lower in patients with deep myometrial invasion (p<0.05). Table 2 shows the performance of ultrasonography, macroscopy, and frozen section for predicting myometrial invasion.

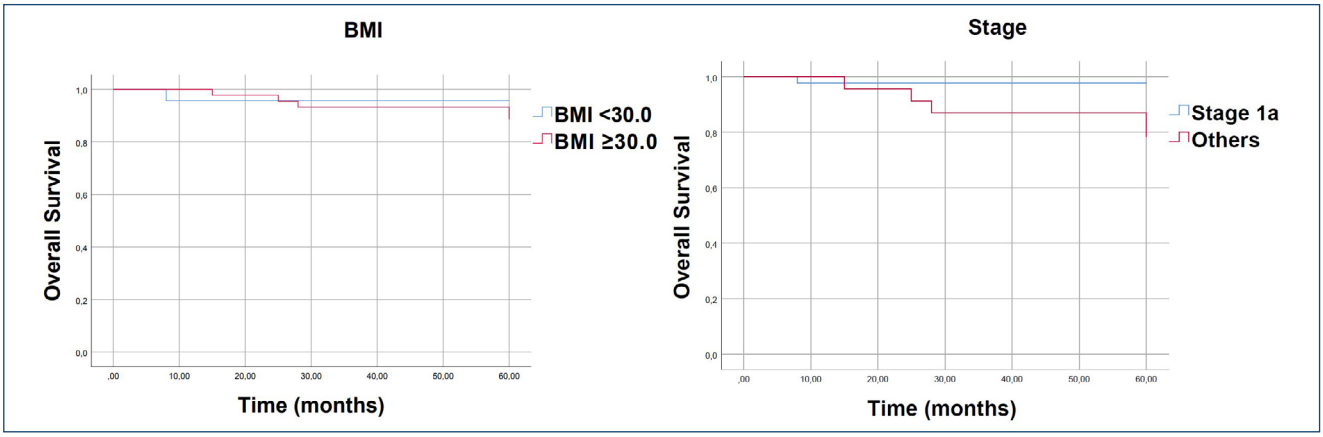

Figure 1. Overall survival rates with respect to body mass index and stage.

Table 1. Demographic and clinical characteristics of the patients with respect to histopathologically confirmed myometrial invasion.

	Myometrial invasion <50% (n=45)	Myometrial invasion ≥50% (n=23)	p
Age (years)	56	60	
Body mass index (kg/m^2)	33.73±7.27	33.73±7.27	0.803
Pre-menopause	11 (100.0%)	0 (0.0%)	0.012*
Post-menopause	34 (59.6%)	23 (40.4%)	
Transvaginal ultrasonography myometrial invasion <50%	39 (79.6%)	10 (20.4%)	0.001*
Transvaginal ultrasonography myometrial invasion ≥50%	6 (31.6%)	13 (68.4%)	
Intraoperative macroscopy myometrial invasion <50%	45 (75.0%)	15 (25.0%)	<0.001*
Intraoperative macroscopy myometrial invasion ≥50%	0 (0.0%)	8 (100.0%)	
Frozen section myometrial invasion <50%	45 (80.4%)	11 (19.6%)	<0.001*
Frozen section myometrial invasion ≥50%	0 (0.0%)	12 (100.0%)	
Five-year survival	97.8%	78.3%	<0.05*

*p<0.05 was accepted as statistically significant.

Table 2. Performance of the methods used for predicting deep myometrial invasion.

	Sensitivity (%)	Specificity (%)
Transvaginal ultrasonography	56	86
Intraoperative macroscopic examination	34	100
Frozen section	52	100

DISCUSSION

Endometrial cancer is usually detected between the ages of 50 and 65 years, with mean age of 60 years during diagnosis[11]. Compatibly, in this study, the mean age of the patients with endometrial cancer was 58.1 years. A Turkish study reported that the mean body mass index of patients with endometrial cancer was 25.8 kg/m^2 [12]. The mean body mass index was significantly higher (33.5 kg/m^2) in this study, and this significant increase might be attributed to the variations in demographic characteristics. It has been claimed that 75% of patients with endometrial cancers are postmenopausal[5,11]. Similarly, in this study, 83.8% of the patients with endometrial cancer were postmenopausal.

Imaging methods such as transvaginal ultrasonography, computed tomography, transvaginal, and magnetic resonance imaging (MRI) are used in the preoperative evaluation of endometrial

cancer[1,4]. The current guidelines put forward by European Society of Gynecological Oncology, European Society for Radiotherapy and Oncology, and European Society of Pathology recommend MRI for predicting deep myometrial invasion in affected patients[13].

Dietz et al. claimed that the sensitivity and specificity of transvaginal ultrasonography were 92 and 50%, respectively, for predicting myometrial invasion in patients with endometrial cancer[14]. Ozdemir et al. yielded the sensitivity and specificity of transvaginal ultrasonography as 86 and 90%, respectively, for predicting myometrial infiltration[15]. Köse et al. assigned the sensitivity and specificity of preoperative transvaginal ultrasonography as 91 and 81.8%, respectively, for predicting myometrial invasion[12]. Savelli et al. found the sensitivity and specificity of transvaginal ultrasonography as 75 and 89%, respectively, for predicting myometrial infiltration[16]. Similarly, in the present study, the sensitivity and specificity of preoperative ultrasonography were 56 and 86%, respectively, for predicting deep myometrial invasion. The relatively lower sensitivity of ultrasonography in this study can be due to the differences in the technical qualities of sonographic equipment.

Intraoperative macroscopic examination can be adopted as an approach for predicting myometrial invasion in endometrial cancer. Pineda et al. stated that the sensitivity and specificity of macroscopy were 78.9 and 90.4%, respectively, for predicting myometrial infiltration[17]. Mavromatis et al. specified the sensitivity and specificity of macroscopic examination as 75 and 92%, respectively, for predicting myometrial invasion[18]. Alcazar et al. found the sensitivity and specificity of macroscopy as 71 and 91%, respectively, for predicting myometrial infiltration[19]. In this study, the sensitivity and specificity of intraoperative macroscopy were calculated as 34 and 100%, respectively, for predicting deep myometrial invasion in endometrial cancer patients. Variations in the professional knowledge and skills of the pathologists might be the underlying reason for the relatively lower sensitivity of intraoperative macroscopic examination in this study.

The sensitivity and specificity of frozen section were designated as 85 and 97%, respectively, for predicting myometrial invasion in endometrial cancer[19]. Another study noted that the sensitivity and specificity of frozen section were 92% for predicting myometrial infiltration[16]. Surprisingly, the sensitivity of frozen section was significantly lower, but the specificity of frozen section was significantly higher than that of MRI for predicting myometrial invasion[20]. In the present study, the sensitivity and specificity of frozen section were 52 and 100%, respectively, for predicting myometrial invasion in endometrial cancer. The inconsistencies in histopathological examination might be the cause for the relatively lower sensitivity of intraoperative macroscopy reported in this study.

The overall survival rate was 85% for endometrial cancer patients[21]. Accordingly, the 5-year disease-free and overall survival rates of these patients were denoted as 95.2 and 96.4%, respectively[22]. Although the 5-year survival rate changed between 74 and 91% for stage 1 and stage 2 tumors, this number decreased to 20 to 26% for stage 4 endometrial cancer[23,24]. In accordance with previous studies, the overall survival rate was 91.2% and overall survival was significantly lowered in endometrial tumors with deep myometrial invasion.

CONCLUSION

This study suggests that transvaginal ultrasonography remains the first-line modality for the assessment of patients with endometrial cancer. The low cost, non-invasive nature, and widespread availability of transvaginal ultrasonography are its major advantages. However, the strength of the present study is limited by its retrospective design, relatively small cohort, relatively shorter follow-up period, and lack of data related to advanced imaging techniques.

Endometrial cancer is the most common gynecological cancer in developed countries. This study aimed to compare the effectiveness of preoperative transvaginal ultrasonography, intraoperative macroscopic examination, and frozen section for predicting deep myometrial invasion in endometrial cancer. Transvaginal ultrasonography and intraoperative frozen section were found to have similar sensitivity and specificity for predicting deep myometrial invasion. Preoperative transvaginal ultrasonography appears as an effective approach for predicting endometrial cancers with deep myometrial invasion.

AUTHORS' CONTRIBUTIONS

CYO: Data curation, Project administration, Resources, Writing – original draft. **EUT:** Data curation, Investigation, Supervision, Validation, Writing – review & editing. **TO:** Formal Analysis, Writing – review & editing. **OTY:** Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

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Changes in body mass index-z scores in 3-year-old children during the COVID-19 pandemic: a 2-year retrospective cohort study

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SUMMARY

OBJECTIVE: Given how dramatically the pandemic has affected food systems, the economy, and the daily lives of children over the past 2 years, the potential impact of the pandemic on childhood obesity requires careful investigation. The aim of this study was to investigate the change in body mass index z-score in 3-year-old children and the inducing factors during the pandemic period.

METHODS: The body mass index z-scores of all children participating in the study were calculated at the beginning of the pandemic (3-year-old body mass index z-score) and in its second year (5-year-old body mass index z-score).

RESULTS: This study, conducted during the 2-year pandemic period, found a strong association between the body mass index z-scores of children aged 3 and 5 years. The mean body mass index z-score increased between these time points for both boys and girls (p=0.013; p=0.034). In two different linear regression models created for the change in body mass index z score, gestational weight gain was found to be related. The regression coefficients (95% confidence intervals) and corresponding p-values were 0.580 (0.217–0.944) and p=0.002 for model 1, whereas they were 0.585 (0.217–0.961) and p=0.002 for model 2.

CONCLUSION: This study showed an increase in body mass index z-scores in early childhood period during the COVID-19 pandemic. To prevent this increase, new strategies should be developed by considering the changes brought by the pandemic period.

KEYWORDS: Childhood obesity. COVID-19. Body mass index. Pandemic.

INTRODUCTION

Childhood obesity is one of the most serious public health problems of the 21st century and it requires immediate preventive measures[1]. The prevalence of overweight and obesity among children under 5 years of age has continued to rise, increasing from an estimated 30.3 million (4.9%) children in 2000 to 38.3 million (5.6%) children in 2019, according to the United Nations Children's Fund, World Health Organization (UNICEF/WHO), and The World Bank Group report[2]. The substantial annual increases in body mass index (BMI) among adolescents with obesity occur between the ages of 2 and 6 years.

The global pandemic declared by WHO in March 2020 has led to significant changes in daily life for children, youth, and their families, with specific recommendations and restrictions varying between countries[3]. Similar to other countries, Turkey also restricted crowded areas, social gatherings, sports activities, and playgrounds and closed schools[4]. This situation caused a lack of physical activity, sleep disorders, and changes in eating habits, which are among the important risk factors for early childhood obesity[5].

Although a few recent studies[6,7] have shown that the pandemic period creates a risk for obesity by causing lifestyle changes in children, there is no study that measures the BMI z-scores in children. Many variables can contribute to childhood obesity, including behavioral, genetic, and environmental factors. Studies show that factors such as maternal BMI, maternal smoking, gestational weight gain (GWG), and gestational diabetes have an impact on early childhood obesity[8]. While there are studies dealing with lifestyle changes during the pandemic period in the literature, there is a lack of comprehensive research that includes other risk factors.

In this study, which is, to the best of our knowledge, the first to show the changes in BMI in early childhood during the COVID-19 pandemic period, we investigated the change in BMI z-scores during the 2-year pandemic period and the factors affecting it.

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METHODS

Study population

This extensive retrospective cohort study was conducted in 42 family medicine centers located in Rize, Turkey. Data collection centers are spread over a wide geographical area, both urban and rural. This study included 289 children aged 3 years (born between January 1, 2017 and March 31, 2017) at the onset of the pandemic. The data of 266 children were analyzed, excluding the children who did not want to share data, had missing follow-up information, or could not be reached.

Children included in this study were evaluated regularly according to the official monitoring protocol of the Family Medicine Practice of Turkey until the age of 5 years. According to the protocol, children aged 3–5 years were monitored regularly at least 12 times. Family Medicine Information Systems (FMIS) are programs in which the follow-up information of pregnant women and children is recorded during face-to-face interviews in accordance with the authority and responsibilities of Family Physicians in Family Medicine.

Potential confounding variables

Potentially confounding variables measured were child's gender, age in months, birth weight, birth height, birth week, nutrition in the first 6 months, maternal gestational age, mode of delivery, maternal weight gained during pregnancy, maternal pre-pregnancy body mass index, smoking status during pregnancy, educational status of parents, and socioeconomic status.

Weight gained during pregnancy

Gestational weight gain is calculated by subtracting pre-pregnancy weight from maternal weight at the time of delivery and categorized according to the recommendations of the National Research Council and the Institute of Medicine[9]. Underweight, normal weight, overweight, and obese mothers who gained 12.7–18.1, 11.3–15.9, 6.8–11.3, and 5.0–9.1 kg, respectively, were regarded as adequate GWG, whereas those gaining weight above or below specified values were categorized as excessive or inadequate, respectively.

Children's body mass index z-score analysis

The BMI z-score is based on the WHO growth standards, which are age- and sex-standardized measures of adiposity in children, and it represents the optimal growth of children. The BMI z-scores of all children participating in this study were calculated at the beginning of the pandemic (3-year-old BMI z-score) and in its second year (5-year-old BMI z-score)[10]. We categorized the pre-pandemic children according to their BMI z-scores (BMI-for-age z-score cutoff points of <-2.0, >1.0, >2.0 and >3.0 are recommended by WHO to classify children aged 0–5 years as wasted, risk of overweight, overweight, and obese, respectively).

Height and weight were used to calculate BMI (kg/m^2), which was converted to BMI z-scores using the US Centers for Disease Control and Prevention growth reference.

Statistical analysis

The distribution of the mothers' sociodemographic characteristics and some clinical characteristics of the children were calculated alongside the 3-year-old and 5-year-old BMI z-scores of the children. The categorical variables were expressed in numbers and percentages, and the numerical variables were expressed as mean, standard deviation, median, and interquartile range (IQR). Linear regression analysis was used to determine the factors affecting the BMI z-score, and two models were designed for the analysis. In the first model, a set of confounding variables consisted of the child's gender, type of feeding in the first 6 months, mode of delivery, educational status of parents, socioeconomic status, and GWG. By including COVID-19 status (positive), kindergarten attendance, screen time, and fast-food nutrition variables to the previous confounding set, the second model was created. Data were analyzed using the SPSS 22.0 software package, and 0.05 is used as the significance level for all analyses.

Ethical procedure

Necessary written approvals were obtained from the local ethics committee (dated 09.05.2022, with decision number 2022/106). Patient informed consent forms providing all details of the study were given to patients, and their relatives were informed in detail about the study and their written consent was obtained.

RESULTS

Parent and child characteristics

The birth weight of the children included in the study was 3,373.15(±475.88) g. Of note, 60.2% (n=160) of the children were only breastfed for the first 6 months and 49.6% (n=132) of them were born through vaginal delivery. During the pandemic period, 27.8% (n=74) of them had COVID. The mean age of mothers was 30.74±5.54 years, and their average pre-pregnancy BMI was 25.96±4.48 kg/m^2.

When we calculated the mean BMI z-scores of all the children participating in the study, we determined a significant increase in these scores from 3 to 5 years of age, regardless of gender (p=0.034; p=0.013). While analyzing the nutrition of children, we also ascertained that BMI z-scores increased significantly during the pandemic period for those who started to receive supplementary food before 6 months. In contrast, the BMI z-score increased substantially for both the COVID and non-COVID groups (Table 1).

In Table 2, we utilized odds ratios from a multinomial linear regression model that enabled adjustment for the possible influence of potentially important covariates. In two

Table 1. Relationship of 3-year-old body mass index z-score and 5-year-old body mass index z-score with risk factors.

	3-year-old BMI z-score	5-year-old BMI z-score	p*
All group	0.38±1.23	0.68±1.50	**<0.001**
Gender			
Female	0.26±1.01	0.49±1.30	**0.034**
Male	0.50±1.41	0.88±1.66	**0.013**
Infant nutritional status (First 6 months)			
Exclusive breastfeeding	0.57±1.34	0.80±1.51	0.152
Not exclusive breastfeeding	0.25±1.14	0.61±1.49	**0.002**
Type of birth			
Vaginal delivery	0.25±1.22	0.65±1.47	**0.003**
Cesarean section	0.51±1.23	0.71±1.53	0.106
History of COVID-19			
Yes	0.45±1.29	0.81±1.66	**0.031**
No	0.35±1.21	0.63±1.43	**0.011**
Kindergarten attendance			
Yes	0.63±1.26	0.78±1.50	0.331
No	0.29±1.21	0.65±1.50	**0.002**
Possibility of outdoor activities			
Yes	0.40±1.18	0.73±1.43	**0.006**
No	0.34±1.30	0.62±1.58	0.065
Gestational weight gain status			
Excessive	0.47±1.15	1.06±1.43	**<0.001**
Adequate-inadequate	0.29±1.30	0.33±1.47	0.823
Smoking during pregnancy			
Yes	0.70±1.39	1.04±1.53	0.283
No	0.37±1.22	0.67±1.50	**0.002**
Mother's educational status			
Middle school or below	0.15±1.25	0.54±1.47	**0.012**
High school or above	0.49±1.20	0.76±1.51	**0.024**
Father's educational status			
Middle school or below	0.33±1.25	0.52±1.35	0.234
High school or above	0.39±1.22	0.73±1.54	**0.002**
Socioeconomic status			
Low	0.38±1.38	0.49±1.51	0.681
Normal/high	0.38±1.21	0.71±1.49	**0.001**

*Wilcoxon test. Bold indicates statistically significant values.

Table 2. Linear regression predictors of follow-up body mass index z-score change for 3–5 years.

	BMI z-score change					
	Model 1			Model 2		
	b	95%CI	p	b	95%CI	p
Gender (male)	0.075	-0.284–0.434	0.681	0.124	-0.238–0.486	0.500
Infant nutritional status (first 6 months) (not exclusive breastfeeding)	-0.139	-0.512–0.234	0.465	-0.127	-0.502–0.248	0.505
Type of birth (Cesarean section)	-0.243	-0.607–0.121	0.190	-0.245	-0.613–0.123	0.192
Mother's educational status (high school or above)	-0.167	-0.571–0.236	0.415	-0.155	-0.561–0.251	0.453
Father's educational status (high school or above)	0.151	-0.294–0.596	0.504	0.138	-0.310–0.585	0.545
Socioeconomic status (normal/high)	-0.020	-0.673–0.633	0.951	0.029	-0.628–0.686	0.931
Gestational weight gain status (excessive)	0.580	0.217–0.944	**0.002**	0.585	0.217–0.961	**0.002**
History of COVID-19 (yes)	–	–	–	0.103	-0.298–0.503	0.615
Kindergarten attendance (yes)	–	–	–	-0.242	-0.656–0.171	0.250
Screen time (increased)	–	–	–	-0.050	-0.420–0.320	0.789
Sleep duration (decreased)	–	–	–	-0.103	-1.024–0.817	0.825
Fast-food nutrition (increased)	–	–	–	-0.462	-0988–0.063	0.085

Bold indicates statistically significant values.

different linear regression models created for the change in BMI z-score, weight gain during pregnancy was found to be related. Regression coefficients (95% confidence intervals) and corresponding p-values were 0.580 (0.217–0.944) and p=0.002 for model 1, whereas they were 0.585 (0.217–0.961) and p=0.002 for model 2. No relationship was found in terms of gender, nutrition in the first 6 months, mode of delivery, educational status of parents, socioeconomic status, having COVID, kindergarten attendance, screen time, sleep duration, and fast-food nutrition.

In Figure 1, we showed the changes in weight category of 3-year-old children when they reached the age of 5 years. We observed that out of 182 normal-weight children, 36 were at risk for overweight, 15 were overweight, and 4 were obese. Other transitions between groups are shown in Figure 1.

DISCUSSION

This study, conducted during the 2-year pandemic period, found a strong association between BMI z-scores of children aged 3 and 5 years. The mean BMI z-score increased between these time points for both boys and girls.

The pandemic period brought about many problems for children in physical, social, and psychological aspects. Factors affecting early childhood obesity introduced by the pandemic period, such as an increase in screen time, decrease in sleep duration, and change in eating habits, added to the factors already presented in the literature, such as genetic factors, socioeconomic status of the mother, maternal pre-pregnancy BMI, GWG, age, and birth weight.

Recent studies[3,6] have shown that screen time increased, physical activity decreased, sleep time decreased, and fast-food nutrition increased in children during the pandemic period. Conversely, some studies[11] have shown that the pandemic period also posed a risk for childhood obesity. Measurement-based values were not used in any of these studies and no confounding factors were considered. This is the first retrospective cohort study based on anthropometric measurements to investigate early childhood obesity during the 2-year pandemic period.

In this study, while investigating the possible reasons for the abovementioned increase in BMI z-score averages during the pandemic period, we analyzed the variables introduced by this period and the risk factors that are not specific to it.

One of the most relevant issues for children during the pandemic was the decreased physical activity and increased sedentary time during the COVID-19 quarantine. The increase in screen time was remarkable in 48.4% (n=129) of the children participating in this study. This finding is mainly due to less time spent outside and online activity engagements in some countries. Other factors could be the use of electronic media devices for keeping the children busy by remote working parents.

Contrary to school-age children and teenagers having longer sleep durations during quarantine, as expressed in some studies[3], there was no change in total sleep duration of children in

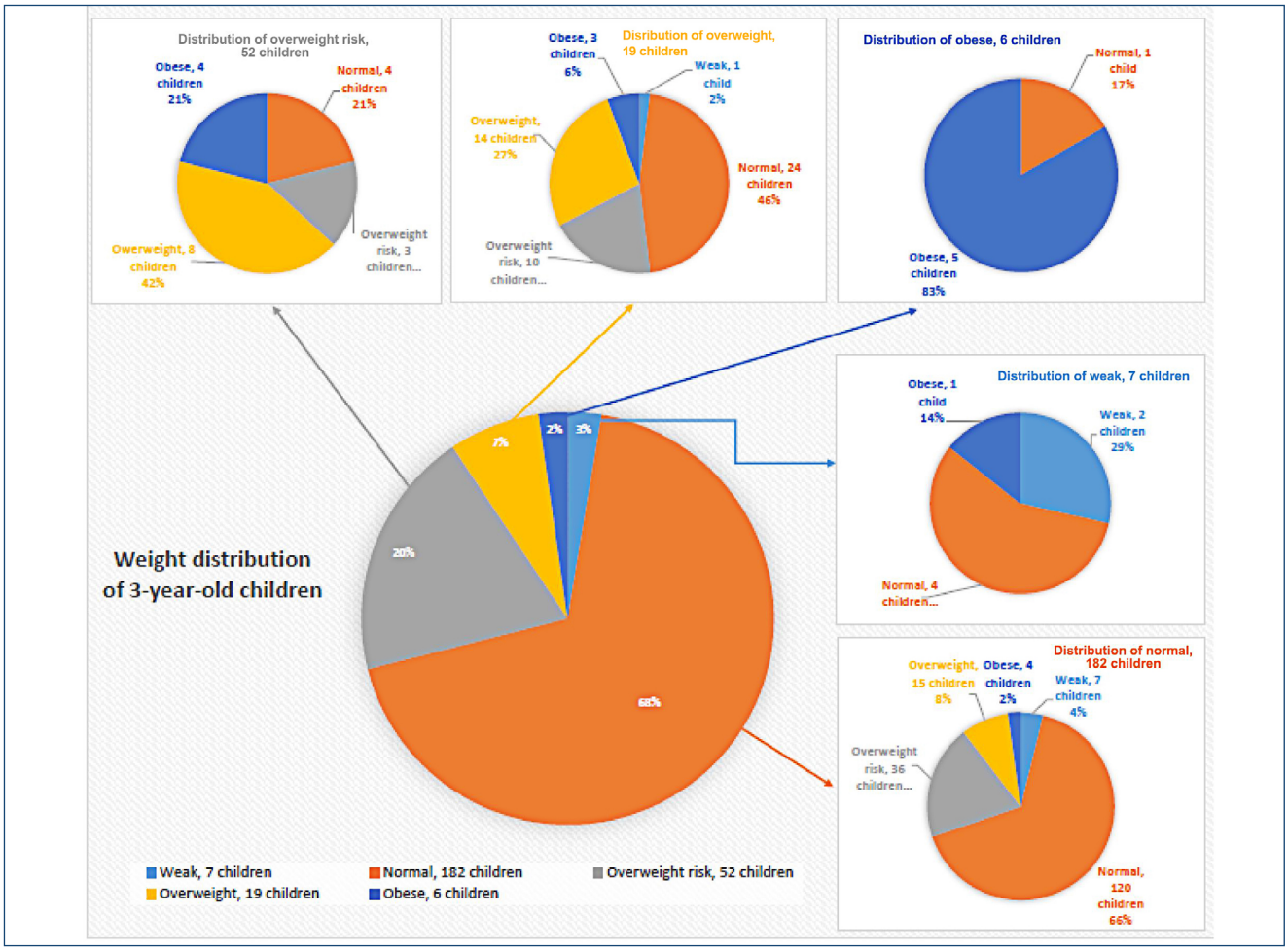

Figure 1. Changes in 3-year-old children's weight categorization at the age of 5 years.

this study. This indication may be the result of the change in bedtimes and wake-up times of children rather than total sleep duration during the pandemic period. Studies have reported a delay in bedtimes and wake-up times than usual for children[12].

There are many studies indicating the effect of GWG on childhood obesity[13]. In this study, we determined that 48.5% of the mothers gained excessive weight according to the criteria of the Institute of Medicine and the National Research Council. In reference to previous studies[14], this high rate of GWG can be explained by the sedentary lifestyle and the change in eating habits induced by the pandemic period. In the linear regression analysis, we found that the increase in BMI z-scores of children (from 3 to 5 years of age) during the pandemic period was the effect of excessive weight gain during pregnancy.

Our study, being the first based on anthropometric measurements in early childhood during the pandemic period, had several strengths. First, it was predicated mostly on quantitative data. Second, the data gathering procedure (anthropometric measurements) was performed by trained research assistants using a standard protocol, thereby reducing probable errors associated with the usage of measurements obtained during clinical care visits and the recall bias from parent-reported measurements. Additionally, data on independent variables were collected both prenatally and postnatally. Thus, reducing recall bias, and especially collecting data in the context of a cohort study that did not focus on obesity reduced the potential for acceptance bias.

There were some limitations in this study. One of the weaknesses of this study was the dependence of the sleep duration data on solely parental feedback. Also, data on dietary intake and physical activity were not quantitative. In addition, the difficulties in both determining screen time exposure and the current validity of screen time measurements were other weaknesses[15].

CONCLUSION

To the best of our knowledge, this is the first study on the assessment of BMI z-scores in early childhood which showed

an increase in these scores for both boys and girls during the COVID-19 pandemic period. Related variables other than GWG were found ineffective via the regression analysis. An increase in research analyzing different confounding variables introduced by the pandemic period will be beneficial for in-depth understanding of the topic.

ETHICS COMMITTEE APPROVAL

Ethics committee approval for this study was taken from the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine with protocol number 2022/106. Date: 09.05.2022.

AUTHORS' CONTRIBUTIONS

CA: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Supervision, Writing – original draft, Writing review & editing. **KU:** Data curation, Project administration, Resources, Software, Visualization. **AK:** Data curation, Methodology, Validation, Visualization. **SK:** Data curation, Formal Analysis, Software.

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ORIGINAL ARTICLE

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Hormonal intrauterine device in women with renal transplantation: a prospective observational study

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SUMMARY

OBJECTIVE: The main objective of this study is to evaluate the rate of continuity and satisfaction with hormonal intrauterine device in renal transplant recipients.

METHODS: This was a prospective observational study. The sample consisted of patients treated at a Family Planning Outpatient Clinic, from August 2016 to September 2021. Information on each patient's age, parity, and associated diseases as well as satisfaction with the method were analyzed. Patients were invited to participate through electronic messages, and the questionnaire included questions about acceptance of the contraceptive method.

RESULTS: A total of 40 patients were included in the study. The mean age of the renal transplant patients was 32.5 years. The mean duration of hormonal intrauterine device use was 37 months. Acceptance of the method was high, with 97.5% of patients remaining on the method for 1 year and 85% of patients using the hormonal intrauterine device at the time of the study. There were no pregnancies or renal transplant complications in the study. Regarding satisfaction with the method, the majority (77.5%) scored 10.

CONCLUSION: Patients were satisfied or very satisfied with the hormonal intrauterine device. Therefore, the continuation rate was high. Furthermore, this contraceptive method proved to be safe and effective in kidney transplant recipients. No complications, graft rejection, or graft failure were observed after intrauterine hormonal device insertion and during follow-up.

KEYWORDS: Renal transplantation. Contraception. Medicated intrauterine devices. Levonorgestrel. Satisfaction.

INTRODUCTION

Chronic kidney disease (CKD) is a severe, progressive, and terminal pathology of the organ, besides being associated with high morbidity and mortality[1]. According to national data, Brazil occupies a prominent position in the world with the absolute number of kidney transplants (among 35 countries), which is almost 6,000 renal transplants per year[2].

Women represent about 47% of organ recipients, and it is estimated that 40% of them are of childbearing age, i.e., between 18 and 49 years. The median age of patients who received transplants in recent years was 37.9 years, ranging from 23 to 55 years[2]. The degree of sexual dysfunction in women and men with CKD ranges from 20 to 80% depending on the site studied. In women, menstrual irregularity and infertility are most commonly reported.

Renal transplantation improves health outcomes and quality of life[3,4]. After transplantation, women are more likely to become pregnant due to the rapid resumption of renal and endocrine function, which improves fertility[4,5]. There is a tendency toward hormonal normalization, leading to an adequate reproductive physiology. Thus, menstruation and ovulation may return 1–2 months after transplantation, thereby increasing the risk of unplanned pregnancy[4,5].

Women are advised to wait 18–24 months before trying to conceive, as this period allows for graft stabilization, institution of immunosuppressive therapy, and completion of infection prophylaxis. This advice is valid if there are no complications and there is a desire to conceive[6-8]. Therefore, because of the short time interval between transplantation and fertility restoration, effective contraception should be discussed, counseled, and started soon after surgery or ideally before surgery[8,9]. These measures would reduce the complications and adverse events that can occur during pregnancy after renal transplantation. Other concerns include the use of antihypertensive and immunosuppressive drugs, which are often unsafe during pregnancy[10-12].

Renal transplant recipients should be counseled to use safe and highly effective methods, including long-acting reversible contraception: hormonal intrauterine device (levonorgestrel), non-hormonal intrauterine device (copper), and subdermal

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implant[9,13-15]. Although there is consensus on the need for appropriate contraceptive methods in solid organ transplant recipients, there is less evidence to support their efficacy and safety[9,14-16]. The World Health Organization (WHO) neither includes organ transplantation among its eligibility criteria nor describes guidelines for its prescription[17].

Given the importance of the issue, the growth in the population of transplanted women, and the lack of studies, we decided to evaluate the effects of the hormonal intrauterine device in renal transplant patients and their quality of life.

METHODS

This was a prospective observational study, with qualitative and quantitative approaches. The sample consisted of patients who attended the Family Planning Outpatient Clinic of Hospital São Paulo, Federal University of São Paulo, from 2016 to 2021 and who accepted the invitation to participate in the research. All kidney transplant patients with hormonal devices who accepted the invitation to the research were included, and only women who did not have knowledge of Portuguese language were excluded.

Data collection was done through medical records and the database of the Family Planning Outpatient Clinic. The main objective was to select and quantify the number of renal transplant recipients who accepted the hormonal intrauterine device as a contraceptive method, thus evaluating its acceptance rate and continuity. In addition, some variables were analyzed within the group in order to characterize the population using hormonal devices, such as age, ethnicity, number of pregnancies, number of children, comorbidities, time of kidney transplantation, complications with transplantation after insertion of the method (rejection of transplantation, occurrence of comorbidities, pelvic infections, etc.), duration of method use, adverse symptoms after its insertion, continuity, and satisfaction.

Patients were invited to participate in the survey through electronic messages. The women who were interested received a free informed consent form that explained the objectives and benefits of the research. Risks associated with participating in research in a virtual environment and by electronic means, such as the limitations to ensure confidentiality and the potential risk of violation, were also mentioned.

Invited patients who agreed to participate received a questionnaire sent by electronic media, containing 16 questions about the knowledge and acceptance of the long-acting reversible contraception methods (through a score from 0 to 10), as well as the possible side effects and its continuity rate. The medical records of each patient were also analyzed.

RESULTS

A total of 290 renal transplant patients were identified in our outpatient clinic who were being monitored. Among them, we evaluated those who chose the intrauterine hormonal device as a contraceptive method, which totaled to 47 patients (16%). The other 243 (83.7%) chose injectable contraceptives, oral contraceptives, or subdermal contraceptive implants. Of the 47 women who chose an intrauterine hormonal device, 40 patients were included in the study. Among the remaining seven patients, three patients were excluded due to data entry errors, and four patients were excluded due to patient refusal, hospital follow-up, and unsuccessful telephone contact.

The age of the patients at the time of the study ranged from 17 to 48 years. The mean age of the patients in the study was 32.5 years. In this group, the majority (60%) were under the age of 35 years. Out of 40 patients surveyed, 18 (45%) identified themselves as white, 17 (42.5%) as mixed race, and 5 (12.5%) as black (Table 1). Among the patients studied, 20 (50%) reported chronic hypertension and 9 (22.5%) reported diabetes mellitus. These were the most common diseases identified in the group. No patient reported the appearance of a new pathology or worsening of comorbidities after intrauterine hormonal device insertion. Regarding obstetric history, 15 were nulliparous (38%), 12 were primiparous (30%), and 13 (33%) were multiparous. The incidence of previous miscarriage in this population was 20% (8 patients) (Table 1).

The time of renal transplantation was analyzed in months. All intrauterine hormonal devices were placed after transplantation. The mean time from transplantation to device insertion was 65 months. Among the patients, only one (2.5%) had the intrauterine hormonal device inserted less than 2 years after

Table 1. Baseline demographic characteristics of 40 patients with renal transplantation and hormonal intrauterine device.

Age (mean)	32.5 years	
	n	%
Race or ethnicity		
White	18	45
Non-white	22	55
Previous pregnancies		
0	15	38
1	12	30
≥2	13	32
Parity		
0	16	40
1	16	40
≥2	8	20

transplantation, 22 patients (55%) between 2 and 5 years after transplantation, and 17 patients (42.5%) more than 5 years after transplantation.

The mean duration of method use was 37 months. Among the 40 patients, the majority (85%) had received an intrauterine hormonal device in 2 years or more previously. Most users had remained with the intrauterine hormonal device for more than 2 years, indicating good acceptability. Out of six patients who were not using the intrauterine hormonal device at the time of data collection, three had expelled and refused reinsertion, two patients opted for removal because of colic, and one patient opted for removal because of irregular vaginal bleeding. Of the expelled intrauterine hormonal device, one was in the first month and two were after 2 years of use (Table 2).

No patient developed graft rejection or graft failure after insertion of the hormonal intrauterine device. Only two patients reported recurrent urinary tract infection as a complication, and there were no pregnancies among women using the hormonal intrauterine device. Thus, the continuation rate in the first year of use was 97.5 and 85% of patients continued to use the method up to the time of the study, demonstrating a good rate of acceptance and continuation. In terms of satisfaction, 97.5% of renal transplant patients were satisfied or very satisfied with the use of this method.

DISCUSSION

This study supports the safety and efficacy of the hormonal intrauterine device in renal transplant patients. A total of 40 patients were analyzed for an average period of 37 months, forming a sample to compile data and results. The most significant study about this topic was published by Juliato et al.[16] with a cohort of 23 patients, which concluded the safety of using this method in kidney transplant recipients, even when taking immunosuppressive drugs. Despite the clear need for contraception after organ transplantation, the WHO does not yet provide guidelines on the medical appropriateness of contraceptive use in solid organ transplant recipients[17].

Table 2. Time of use of the hormonal intrauterine device and adverse symptoms of 40 patients with renal transplantation and hormonal intrauterine device.

Time of use	Months	n	(%)
≤2 years		6	(15)
2–5 years		32	(80)
≥5 years		2	(5)
Mean time	37		
Expulsion		4	(10)
Reinsertion		2	(5)
Adverse symptoms			
Colic pain		5	(13)
Vaginal bleeding		3	(8)
Recurrent urinary infections		2	(5)

In 2009, the American College of Obstetricians and Gynecologists published a committee opinion endorsing and recommending the use of long-acting methods in this group. These guidelines were well-positioned in 2016 by the U.S. Centers for Disease Control and Prevention, which recognized that solid organ transplantation is a condition associated with the risk of serious adverse events in pregnancy, and stated that long-acting reversible contraception is highly effective and may be the best choice for women in these circumstances[18].

A study published by Ramhendar et al.[14] conducted a 10-year retrospective analysis of 11 renal transplant patients using an intrauterine hormonal device and proved that none of them failed the method or had any type of infection. As mentioned in the study by Dumanski et al.[4], the highest rate of clinical complications after renal transplantation occurs in the first year. Therefore, the necessity for contraception should be guided as early as possible in these patients. The ideal would be the introduction of a method even before the renal transplantation. In our study, we observed a delay in guidance and insertion of the method. Of the renal transplant patients who opted for the intrauterine hormonal device in our outpatient clinic, only one patient (2.5%) had undergone renal transplantation less than 2 years ago. The mean time between renal transplantation and hormonal intrauterine device insertion was 65 months in our study.

During the study period, 290 renal transplanted women were followed and 47 (16%) opted for the intrauterine hormonal device. The mean age of our patients was 33 years, and the majority (60%) reported having one or more children. None of them became pregnant during the study period. There was also no deterioration in renal function or graft rejection during this period. Since the first published studies of this contraceptive method, the literature has described high efficacy, tolerability, safety, and acceptance by women regardless of age or parity[19,20].

Regarding the complaints related to the method, the most common ones reported by this group of patients were colics such as abdominal pain and vaginal bleeding, as reported in the studies for general population. The only point that could be highlighted in our study is the recurrent urinary infections

that occurred after insertion of the method in two patients, with no repercussions on renal transplantation.

The satisfaction rate among users of intrauterine hormonal device is high, reaching 92.5% of patients after 6 years[21]. Our data confirmed the high satisfaction rate with 97.5% of satisfied or very satisfied. Another interesting fact is that 92.5% of them would recommend the intrauterine hormonal device to other women, which shows the good acceptance of the method. In addition, 85% of patients continued to use the method, showing a good continuation rate, with a mean time of use of 37 months.

CONCLUSION

Our study showed that renal transplant women benefited from the use of the hormonal intrauterine device because of its high efficacy and low side effects. In addition, this method was well accepted by the patients and proved to be a great option for this group in particular.

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AUTHORS' CONTRIBUTIONS

CAFG: Conceptualization, Project administration, Visualization. FCA: Data curation, Investigation, Validation, Visualization, Writing – original draft. **APO:** Data curation, Methodology, Validation, Visualization. **TENKH:** Formal Analysis, Supervision, Validation, Visualization. **EAJ:** Visualization, Writing – review & editing.

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Effects of kinesiology taping on swallowing functions in newborns with swallowing difficulties: a randomized controlled pilot study

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SUMMARY

OBJECTIVE: This study investigated the efficacy of kinesiology taping application in premature infants with dysphagia.

METHODS: A total of 60 premature newborns (born ≤37weeks' gestational age who reached the age ≥34 weeks of postmenstrual age) with sucking and swallowing problems were randomly assigned to the kinesiology taping group [n=31; 18 males, 13 females; mean postmenstrual age 35.4 weeks (SD 0.9 weeks, range 34–38 weeks)] or control group without kinesiology taping application [n=29; 16 males, 13 females; mean postmenstrual age age 35.6 weeks (SD 1.4 weeks, range 34–40 weeks)].

RESULTS: Kinesiology taping group yielded significant improvement in the oral reflexes (p<0.001) and in the sucking functions including tongue movement, sucking power, number of sucks and sucking pause, maintenance of alertness, jaw movement, tongue cupping, and maintenance of rhythm (p<0.001, p=0.011, p=0.002, and p=0.001, respectively). There was a significant difference in favor of the taping group with respect to the number of neonates whose feeding improved (26 (84%) vs. 7 (24%), p<0.001).

CONCLUSION: The results of this study show that kinesiology taping can be applied as a safe and effective method to improve feeding functions in premature infants with sucking and swallowing difficulties.

KEYWORDS: Kinesio tape. Premature infant. Dysphagia.

INTRODUCTION

Advances in perinatal care and technology have resulted in increased rates of premature newborns, and a greater number of infants are surviving with significant feeding problems[1]. Providing effective oral feeding for adequate growth and development is a prerequisite in the care of premature infants. The prevalence of feeding problems is two times more common in preterm infants compared with full-term infants, and the causes of feeding difficulties are multifactorial[2,3]. Neurosensory and neuromotor pathways organization, cognitive development, and social stimulation of preterm infants are poor; therefore, these infants are at increased risk for impaired sucking, swallowing, and breathing[1,4]. Sucking and swallowing difficulties in premature infants are related to poor nutritional intake, aspiration, and recurrent respiratory illness, requiring frequent hospitalization and increased gastrostomy needs and have a detrimental effect on growth and neurodevelopmental outcomes[5-7].

Kinesiology taping (KT) is widely used in musculoskeletal system, nervous system, sports, and pediatric rehabilitation to reduce pain, facilitate or inhibit muscle function, prevent injuries, improve stability to joints, and provide proprioceptive feedback[8-10]. KT has been shown to improve blood flow in microcirculation and activation of the cutaneous sensory system that provides stimulation to neuromuscular functions[10,11]. Previous studies have examined the effect of KT on pediatric rehabilitation in patients with congenital muscular torticollis and spastic cerebral palsy[12,13]. There is a paucity of data in the literature evaluating the effect of KT on swallowing difficulties. Park et al. demonstrated a new treatment method for dysphagia rehabilitation in adults using KT[14]. As discussed by Lin et al., there is only one case report worldwide that used the KT method on infants suffering from impaired sucking and swallowing[15].

To the best of our knowledge, no randomized control trial has been performed to show the effects of the KT method on infants with sucking and swallowing difficulties. The purpose of this study was to investigate the effects of applying KT for sucking and swallowing problems in premature infants.

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METHODS

Participants

This study was a single-blind randomized controlled study and was performed in the neonatal intensive care unit and neonatal service. A total of 76 premature infants (born ≤37 weeks' gestational age who reached the age ≥34 weeks of post-menstrual age (PMA)) with sucking and swallowing problems were enrolled in the study. The exclusion criteria were (1) the presence of congenital abnormalities and syndromes, (2) infants exposed to drugs and alcohol, (3) infants with central nervous system diseases, (4) infants with chromosomal abnormalities, (5) the presence of musculoskeletal system and skin disorders, (6) newborns who have cardiopulmonary disease affecting the sucking, swallowing, and breathing patterns such as bronchopulmonary dysplasia, and (7) infants whose parents refused to participate.

Ethics considerations

Ethical approval was obtained from the local ethics committee of the University of Health Sciences Turkey, Ankara City Hospital (E2-21-91). Parents were informed about the application of KT, and written informed consent was obtained from each guardian, which followed the ethical principles outlined in the Declaration of Helsinki.

Procedure

Of the 76 participants, 32 were randomized to the KT group and 32 to the control group without KT application as shown in the flowchart (Figure 1). One premature infant discontinued treatment in the KT group, and three premature neonates who required invasive respiratory support or had pneumonia discontinued in the control group. The kinesiology tape (Kinesio® Tex Gold Light Touch; 5 cm×5 m, United States) was applied by a certified physician. Three types of KT were prepared and attached based on Lin et al.: (1) two I-shaped tapes were used for taping on the upper orbicularis oris (3.3 cm long tape) and lower orbicularis oris (5 cm long tape) muscle with pulling force of about 15% to the bilateral corner of the mouth to facilitate lip closure; (2) the Y-shaped tape was attached from the symphysis of the mandible bone to the hyoid bone toward the sternum to improve the elevation of the hyoid bone by inhibiting the sternohyoid muscle and stimulating the mylohyoid muscle; and (3) the masseter muscle was facilitated with tape (separated into three ends under 15% pulling force, mild strength) anchored on the lower border of the zygomatic arch and elongated to the coronoid process of the mandible bone to improve the jaw movement and chewing activity[15]. After applying

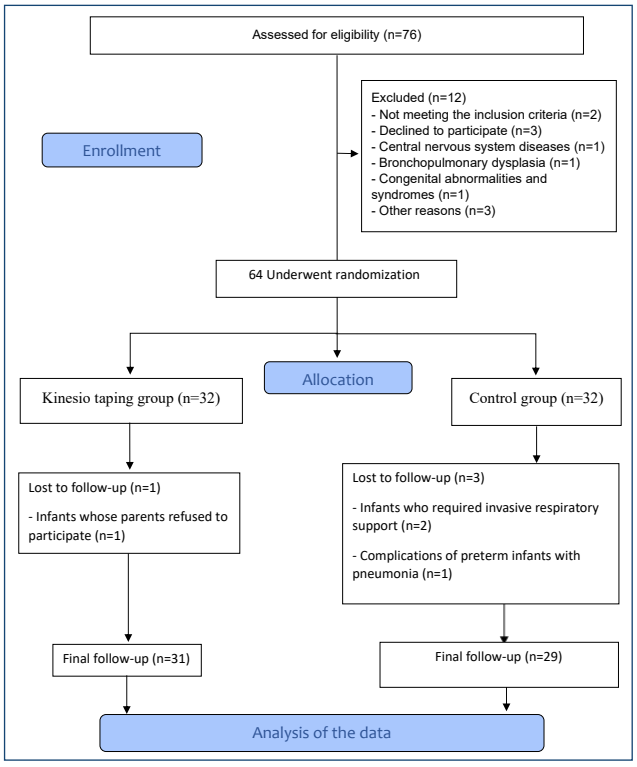

Figure 1. Flowchart of study subjects.

the KT, the tape remained on the skin for 24 h. At the end of 24 h, the tape was removed allowing infants to rest for 24 h. The tape was then applied again in the same way every 48 h. All participants received a total of five taping sessions with 1-day interval for 10 days. Sucking and swallowing functions (i.e., oral posture, oral reflex, sucking, and symptoms) were evaluated before and after the taping application of each session by two experienced speech-language therapists. Lips and tongue posture were assessed for oral posture function; rooting, sucking, and biting reflexes were evaluated for oral reflex; tongue and jaw movements, tongue cupping, sucking power, number of sucks, sucking pause, maintenance rhythm, and state of alertness were recorded for sucking function. Stress signs, accumulation of saliva, apnea, changes in skin color, hiccups, and crying were also noted during the evaluation[16].

Statistical analysis

All data analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, New York, USA). Categorical variables are expressed as counts and percentages, and continuous variables are presented as mean±standard deviation or as median. Categorical variables were compared by the chi-square test or Fisher's exact tests as appropriate. The McNemar test was used to evaluate bivariate categorical data, and the marginal homogeneity test was used to evaluate trivariate categorical data between

two dependent groups. Kolmogorov-Smirnov tests were used to evaluate the distribution of variables. Comparisons of parametric values between the two groups were compared using the independent-samples t-test. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

The study included 60 premature neonates (n=60) (≥34 completed weeks' PMA) with sucking and swallowing difficulties randomized between the KT group (n=31; 18 males, 13 females; mean PMA 35.4 weeks [SD 0.9 weeks, range 34–38 weeks]) and the control group (n=29; 16 males, 13 females; mean PMA age 35.6 weeks [SD 1.4 weeks, range 34–40 weeks]) receiving usual care. The baseline general characteristics of the subjects are shown in Table 1. There was no statistically significant difference between the groups in terms of PMA, gender, method of delivery, number of pregnancies, birth weight, gestational age, blood groups, and initial milk-feeding amounts, indicating that the groups were well-matched.

After 10 days of KT application, a comparison of sucking and swallowing functions in the KT and control groups was done and the details are given in Table 2. Comparison results within the group after the intervention revealed that there were no significant differences in lip and tongue posture activity between the study groups (p>0.05). Similarly, no differences were observed in the infants' stress signs, apneic attacks, changes in skin color, crying, and hiccups. However, oral reflexes were assessed via rooting, sucking, and biting reflexes, with results showing better oral reflexes in the KT group compared with the control group (p<0.001). Also, after 10 days of application, the taping group showed a significant improvement in sucking behaviors including tongue movement, sucking power, number of sucks and sucking pause, maintenance of alertness, jaw movement, tongue cupping, and maintenance of rhythm (p<0.001, p=0.011, p=0.002, and p=0.001, respectively).

Table 1. Baseline characteristics of the participants.

	Control group (n=29)	KT group (n=31)	p-value
Gender			
Male	16 (55%)	18 (58%)	0.821
Female	13 (45%)	13 (42%)	
Method of delivery			
Vaginal	4 (14%)	4 (13%)	0.919
Cesarian section	25 (86%)	27 (87%)	
Number of pregnancies			
First pregnancy	17 (59%)	22 (71%)	0.411
Second pregnancy	11 (38%)	9 (29%)	
Third pregnancy	13 (%)	0	
Birth weight (g)	1,392±340	1,370±341	0.803
Gestational age (weeks)	29.9±1.5	29.8±1.6	0.732
Blood groups			
A Rh positive	19 (65%)	20 (64%)	0.939
A Rh negative	1 (3%)	1 (3%)	
B Rh positive	3 (10%)	2 (6%)	
B Rh negative	1 (3%)	1 (3%)	
O Rh positive	2 (7%)	5 (16%)	
O Rh negative	1 (3%)	1 (3%)	
AB Rh positive	2 (7%)	1 (3%)	
Postmenstrual age at the start of assessment	35.6±1.4	35.4±0.9	0.513
Milk feeding every 2–3 h (oral, mL)	8.2±5.0	9.3±4.0	0.377
Milk feeding every 2–3 h (orogastric, mL)	20.5±7.8	17.6±4.2	0.080

Table 2. Comparison of the results between the kinesio taping and control groups.

	KT group (n=31)	Control group (n=29)	p-value
Evaluation of oral reflex			
Rooting			<0.001
Weak	4 (13%)	22 (76%)	
Present	27 (87%)	7 (24%)	
Sucking			<0.001
Weak	6 (19%)	23 (79%)	
Present	25 (81%)	6 (21%)	
Biting			<0.001
Weak	6 (19%)	17 (59%)	
Present	25 (81%)	12 (41%)	
Sucking function			
Tongue movement			<0.001
Decreased	3 (10%)	22 (76%)	
Adequate	28 (90%)	7 (24%)	
Tongue cupping			0.002
Absent-decreased	8 (26%)	19 (65%)	
Adequate	23 (74%)	10 (35%)	
Jaw movement			0.011
Decreased	8 (26%)	17 (59%)	
Adequate	23 (74%)	12 (41%)	
Sucking power			<0.001
Weak	6 (19%)	22 (76%)	
Strong	25 (81%)	7 (24%)	
Number of sucks and sucking pause			<0.001
<5	2 (6%)	14 (48%)	
5–8	9 (29%)	8 (27%)	
>8	20 (65%)	7 (25%)	
Number of infants whose feeding improved at the end of 10 days	26 (84%)	7 (24%)	<0.001

We evaluated nutritional status by controlling the amount of milk feeding and the infant's dependency on tube feeding in these infants before and after KT application. As a result of the comparison between groups from baseline to 10 days, the KT group showed significant differences in oral feeding and the number of infants whose nutritional status improved was higher in the taping group (26 (84%) vs. 7 (24%), p<0.001).

DISCUSSION

This study is the first single-randomized controlled trial focusing on the effects of KT application in premature infants with sucking and swallowing difficulties. We showed that taping improved the sucking and swallowing performance of premature newborns.

With the development of neonatal intensive care practices, higher rates of survival of premature infants are seen; however, prematurity has led to risk for adverse neurodevelopmental outcomes like feeding difficulty by mouth[1,17]. The pathophysiology of dysphagia in preterm infants is multifactorial and most likely the consequence of neuromotor and neurophysiological dysfunctions such as delayed or not efficient reflexes, hypotonia, poor suck-pharyngeal coordination, and generalized lack of coordination[4,6]. For efficient and safe nourishment,

premature infants need to properly provide coordination of breathing with sucking and swallowing and the interaction of lips, jaw, tongue, palate, pharynx, larynx, and oesophagus[4,18]. Preterm infants with sucking and swallowing problems are at increased risk for prolonged hospitalization, parenteral nutrition, supplemental oxygen, and aspiration pneumonia, with detrimental effects on postnatal growth and dietary intake[1,6,7].

To date, several studies have shown that KT is an effective method in musculoskeletal system, nervous system, sports, pediatric rehabilitation, and various other disorders[8-10]. For example, this technique was performed to investigate the immediate effect of KT on the muscular imbalance in the lateral flexors of the neck for infants with congenital muscular torticollis in pediatric rehabilitation. Likewise, Kaya et al. also demonstrated that KT could increase proprioceptive feedback and improve gross motor function in children with unilateral spastic cerebral palsy[13]. However, few published studies are available with KT that show the use of the KT method for dysphagia. Recently, Jung et al. suggested that taping may promote oropharyngeal muscle thickness and could be a potentially therapeutic clinical exercise for stroke patients with dysphagia[19]. It has also been reported that KT application pulls the hyoid bone and larynx downward which improves activation of the suprahyoid muscle during swallowing in adults with dysphagia rehabilitation[14]. One recent publication indicated the effectiveness of KT method in drooling and speech intelligibility in children with oral dysphagia[20]. Additionally, another recent case report demonstrated the effect of KT on premature infants with sucking and swallowing difficulties[15].

The act of feeding and swallowing consists of four phases, namely, oral phase, triggering of the swallowing reflex, pharyngeal phase, and esophageal phase[21]. The suprahyoid muscle, consisting of the geniohyoid, mylohyoid, digastric, and stylohyoid muscles, plays a critical role in swallowing function in the pharyngeal phase[22]. The taping facilitates muscle activation and is related to increased motor unit activation that reflects an increase in the strength of the muscle[23,24]. As such, it has been suggested that KT induces muscle activation by adding load to the suprahyoid muscles during swallowing for patients with dysphagia[14].

Lin et al. indicated that KT could easily attach to the skeletal muscles to induce the orbicularis oris muscle for lip closure, the masseter muscle for jaw movement and chewing activity, and the mylohyoid muscle for hyoid bone elevation and inhibit the sternohyoid muscle activity for better sucking and swallowing functions[15]. Likewise, our results confirmed the influence of taping on sucking and swallowing difficulties in premature infants. We agree with Lin et al. on the possible underlying mechanism of using KT in the improvement of sucking and swallowing functions via muscle facilitation and inhibition[15].

The results of our study should be assessed with some limitations. First, this is a single-center study with a relatively small sample size. Second, we could not use a video fluoroscopic swallow study or a fiberoptic endoscopic evaluation for detecting dysphagia, which is more reliable compared with clinical examination alone. Therefore, further prospective and randomized clinical trials are required to assess the effectiveness of the KT method.

CONCLUSION

This is the first randomized controlled study using the KT method in dysphagia rehabilitation in premature infants and demonstrated that KT resulted in improvement in sucking and swallowing functions. The taping is a simple, inexpensive, and less traumatic method that may be valuable in the rehabilitation of dysphagia for premature newborns.

AUTHORS' CONTRIBUTIONS

TÖÇ: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **PB:** Conceptualization, Formal Analysis, Investigation, Writing – review & editing. **CT:** Data curation, Resources, Writing – review & editing. **MK:** Conceptualization, Software, Writing – review & editing. **FÇ:** Conceptualization, Software. **EY:** Resources, Writing – review & editing.

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ORIGINAL ARTICLE

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Cytogenetic changes in oral mucosal cells of human immunodeficiency virus-infected children and adolescents undergoing antiretroviral treatment

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SUMMARY

OBJECTIVE: The objective of this study was to evaluate possible cytogenetic changes in children and adolescents with human immunodeficiency virus on antiretroviral therapy, through the micronucleus test in oral mucosa.

METHODS: This was a prospective study consisted of 40 individuals, of whom 21 comprised the human immunodeficiency virus group and 19 comprised the control group. Children and adolescents with human immunodeficiency virus were enrolled. The inclusion criteria were <18 years old and consent in participating in the study. The exclusion criteria were the presence of numerous systemic comorbidities, oral lesions, the habit of smoking, alcohol consumption, and X-rays or CT scans taken within 15 days prior to sample collection. A gentle scraping was performed on the inner portion of the jugal mucosa on both sides. A total of 2,000 cells per slide were analyzed for the determination of mutagenicity parameters as follows: micronuclei, binucleation, and nuclear buds. For measuring cytotoxicity, the following metanuclear changes were evaluated: pyknosis, karyolysis, and karyorrhexis, in a double-blind manner. The repair index was also evaluated in this setting.

RESULTS: The human immunodeficiency virus group showed high frequencies of micronuclei (p=0.05), binucleated cells (p=0.001), and nuclear buds (p=0.03). In the cytotoxicity parameters, represented by the cell death phases, there was an increase with statistical difference (p≤0.05) in the karyorrhexis frequency (p=0.05). Additionally, repair index was decreased in the human immunodeficiency virus group.

CONCLUSION: These results indicate that human immunodeficiency virus -infected individuals undergoing antiretroviral therapy have cytogenetic changes in oral mucosal cells.

KEYWORDS: Child. DNA damage. HIV. Micronucleus tests. Mouth mucosa.

INTRODUCTION

Currently, 79 million people have been infected worldwide with the human immunodeficiency virus (HIV), whose predilection for immune system cells, which induces acquired immunodeficiency syndrome (AIDS), has been responsible for the death of 39 million people since the beginning of the epidemic[1]. Still, it is responsible for 88% of contaminations of children up to 13 years. From this age, the main route of contamination is sexual. During the past 10 years, there has been an increase of 64.9% in young males aged 15–19 years, while there has been a significant decrease among women in this age group[2].

Antiretroviral therapy (ART), started in the late 1980s, has been constantly evolving, acting especially on the replication of the virus in several stages and combining different classes of antiretrovirals. Antiretroviral drugs are classified according to their mechanism of action. There are more than 25 drugs divided into six types: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, integrase inhibitors, and entry inhibitors. In fact, ART has shown a reduction in mortality and a significant increase in survival. It also shows an improvement in the quality of life and suppression of viral load in many cases, which decreases the chance of transmission, preventing vertical transmission[3,4]. In 2004, a study reported that only 26% of children achieved complete viral suppression with 72 weeks of ART[5], in contrast to the percentage observed by Gulick et al.[6] whose remission in adults was 89% after 48 weeks of ART treatment. In the same study, Aboulker et al.[7] demonstrated 30% of selection of HIV resistance mutations in children, leading to virological failure, and emphasized the

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importance of early initiation of ART in children. In Europe and the United States, the infant mortality rate fell between 80 and 90% after the introduction of ART, and although it is considered a chronic disease at present, it is estimated that the survival of these children is 30 times lower than a healthy child[8]. However, metabolic, neurological, cardiovascular, renal, and cancer disorders are the complications not related to AIDS, but related to the set of aging conditions mediated by HIV, or even by the persistent inflammatory immune process, even if under treatment[9,10].

Micronuclei (MN) are small fragments of nuclei (DNA), present in the cytoplasm of nucleated cells, and are used as a sensitive biomarker of chromosomal damage, genome instability, and mutagenicity[11,12]. MN originate during cell division, from a damage that exceeds the repair capacity, which can lead to the loss of an entire chromosome (aneugenic event), or a chromosome fragment (clastogenic event), and that in the final phase of cell division, telophase, receive a nuclear envelope, giving a similar appearance to the nucleus with a smaller size in relation to the main nucleus[13]. In the 1980s, Stich and Rosin proposed a modification capable of identifying such MN in exfoliated cells of the oral mucosa[14], with the advantage of being a less invasive test and easy to perform in relation to other genetic tests. This methodology has since proved to be an important biomarker of effect, versatile, and low cost, which focuses on prevention, predicting an interaction between a chemical, physical, or biological substance, with biological receptors, ideally when there is no disease. It should be noted that these are not diagnostic tests[15], but internationally recognized tests, which are considered robust, simple, and amenable to automation, with established regulatory guidelines[16]. Based on the information presented, the objective of this study was to evaluate possible cytogenetic changes in children and adolescents with HIV on ART, through the micronucleus test in oral mucosa.

METHODS

Casuistics

The study was approved by the Institutional Human Ethics Committee from Federal University of São Paulo, under the protocol 0485/2019. All the legal guardians of participants signed the informed consent form and participants signed the assent form.

This prospective study consisted of 40 individuals; of whom 21 comprised the HIV group and 19 comprised the control group. All participants received detailed information about the project and the consent form was delivered to children and adolescents (<18 years), after being signed by their respective guardians. Children and adolescents (aged from 0 to 18 years), with HIV were enrolled, who were regularly monitored at the Specialized Child Care Service (SAE infantil) in the city of Santos – SP, Brazil, and whose total was 21 people from August to December, 2019. The inclusion criteria were <18 years old and consent in participating in the study. The exclusion criteria were the presence of systemic comorbidities, oral lesions, the habit of smoking, alcohol consumption, and X-rays or CT scans taken within 15 days prior to sample collection. A single examiner, a dentist, collected, stained, and examined the unidentified samples. The control group was enrolled by direct approach randomly in public places in the city of Santos – SP. Exclusion criteria were similar to that of HIV group.

Micronucleus test in oral cells

The buccal mucosal MN test followed the protocol described by Belien et al.[17] With the aid of a wooden spatula previously moistened in saline solution, a gentle scraping was performed on the inner portion of the jugal mucosa on both sides, for approximately 10 times each side. The material was deposited on a clean and dry histological slide. The slides were stained by Feulgen-Fast-Green technique. A total of 2,000 cells per slide were analyzed, at 1,000´ magnification, for the determination of MN, binucleation (BN), and nuclear buds (NB), and cytotoxicity parameters such as pyknosis (PK), karyolysis (KL), and karyorrhexis (KR) in a double-blind manner. The correct identification of such parameters was established by Bolognesi et al.[18]. For this purpose, the following criteria were established for the correct identification of cytogenetic changes of MN: (1) intact main nucleus and cytoplasm; (2) one-third diameter of the main nucleus; (3) similar stain and texture of the main nucleus; and (4) MN in the same focus as that in the main nucleus; KR: the nucleus may also exhibit extensive fragmentation indicative of advanced nuclear fragmentation; BN: two main nuclei within a single cell and the nuclei are of similar size and staining intensity; NB: the main nucleus has a sharp constriction forming a bud of nuclear material being attached to the main nucleus by a narrow or wide nucleoplasmic bridge; PK: the nucleus is small and shrunken with a diameter that is approximately one-third of that in a fully differentiated cell being uniformly and intensely stained; and KL: they do not have a DNA-containing nucleus or other structures that stain with Feulgen.

The repair index (RI), proposed by Ramirez and Saldanha[15], represented by the formula RI=(KL+KR)/(MN+NB), was also evaluated in this setting.

Statistical analysis

All data were submitted to the normalization using Kolmogorov-Smirnov test. After that, non-parametric data were confirmed by all data collected in this setting. The test used to evaluate the metanuclear alterations and DNA RI between the control group and HIV was the non-parametric Mann-Whitney U test. The statistical significance level was set at 5%. The statistical analysis was conducted by the Bio Stat software (version 5.0, Maringá-Brazil).

RESULTS

In the HIV group, there was an exclusion of only one transsexual teenager, who was a smoker and also used other drugs such as LSD ((lysergic acid diethylamide) and ecstasy (3,4-methylenedioxy-methamphetamine). The distribution was 9 boys and 11 girls, all of whom reported good eating habits including fruits, except the 4-month-old baby who used milk formula. Only one adolescent reported occasional use of marijuana and eight reported the use of mouthwash. Only 4 cases were in treatment between 1 and 3 years, and the other 16 cases were in treatment from the beginning of life. Regarding the control group, all participants were included and the distribution was 8 boys and 11 girls, of whom 6 reported using mouthwash and none were using any medication. The groups are represented in Table 1.

The HIV group presented an increase in statistical difference ($p \leq 0.05$) in relation to the control group in the parameters of mutagenicity, the frequency of MN ($p=0.05$), BN ($p=0.001$), and NB ($p=0.03$), as shown in Table 2.

In the cytotoxicity parameters, there was an increase in statistical difference in the frequency of KR ($p=0.05$). KL and PK showed no significant increase ($p>0.05$), as shown in Table 2. Finally, the RI shown in Table 2 suggests a higher repair capacity in the control group when compared to the HIV group.

DISCUSSION

Our results demonstrated that children infected with HIV undergoing ART therapy possess cytogenetic damage in the oral mucosa as depicted by increasing mutagenicity, cytotoxicity, and low DNA repair capacity. It is important to highlight that the success of ART is undeniable in relation to the higher life expectancy and quality of life, giving chronicity status to the infection caused by HIV. However, the side effects of ART are well documented and others are still being studied. There are 12 types of drugs used in this HIV group, in different conjugations, always using a cocktail of at least 3 drugs per individual, according to the guidelines commonly used for the management of HIV infection. Nucleosides reverse transcriptase inhibitor drugs are essential constituents that make up ART, and patients in general receive two drugs of this class in combination with a third active drug of another class[19]. This protocol may change according to the body response, from the viral load and clinical response, and which can be influenced by both virus mutations and individual interruptions or adverse reactions in treatment. In a study with mice, alterations such as hepatocellular adenomas, carcinomas, and pulmonary alveolar/bronchiolar adenomas were reported with the use of tenofovir and

Table 1. Demographic characteristics of study participants.

Parameters	Control group (n=19)	HIV group (n=21)
Mean age	6.9 (4.9)	13.1 (4.72)
Gender	8/11 M/F	9/11 M/F
Time of therapy (years)	–	9.3+6.1
Time of infection (years)	–	9.4+6
Educational level		
Primary level	19	21
Secondary level	0	0
Ethnicity		
Black	0	0
White	14	11
Mixed	5	10
Use of mouthwash	6	8
Use of illicit drugs	0	1

Table 2. Total number [Median (Min–Max)] of oral cells presenting genotoxicity, cytotoxicity, and DNA repair index in children infected with human immunodeficiency virus undergoing antiretroviral therapy

Groups	Normal	Karyolysis (KL)	Karyorrhexis (KR)	Pyknosis (PK)	Micronucleus (MN)	Binucleation (BN)	Nuclear bud (NB)	(KL+KR)/ (MN+NB)
Control (n=19)	1,633 (1,556–1,748)	199 (50–328)	21 (6–34)	138 (64–285)	0 (0–1)	0 (0–1)	0 (0–1)	227 (31–309)
HIV (n=20)	1,618 (1,450–1,704)	220.5 (175–266)	43.5 (34–53)*	122.5 (63–182)	1.5 (1–2)*	1.5 (1–2)*	0 (0–0)	91 (33–309)*

*$p \leq 0.05$ when compared to control.

efavirenz[20], but this risk with tenofovir and entecavir in humans was not evident in the recent review published by Tseng et al.[21] Nephrotoxic effects, liver disease, and bone hypomineralization have been described in nucleoside reverse transcriptase inhibitor drugs[19]. In this study, the HIV group presented statistical difference in all mutagenicity parameters (MN, NB, and BN), in relation to the control group of healthy children and adolescents submitted to ART.

Regarding cytotoxicity, parameters were also altered, specifically in KR, which may suggest that the organism is constantly being challenged, by the mechanisms of cell cycle control and tissue death. We can still observe that even with an increase in the rate of cell death, which could mask the presence of mutagenic alterations, MN, NB, and BNs were increased in the HIV group, which suggests a high mutagenicity detectable by the proposed methodology. These results were confirmed by the decrease in the efficiency of the repair system in the experimental group. Despite few studies involving children, in 2007, Witt et al.[22] evaluated the chromosomal damage of infants exposed to ART by transplacental route and observed increased MN in erythrocytes in these infants born to seropositive mothers, who used zidovudine during pregnancy, and were also prophylactically medicated for 6 weeks after birth. The genotoxicity and mutagenicity of this drug had already been described in other studies in vitro and in animal models[23]. In 2013, Olivero et al.[24] observed that the use of ART, with reverse transcriptase inhibitor drugs (zidovudine, lamivudine, abacavir, and nevirapine) in the offspring of pregnant monkeys not carrying HIV, which were medicated during pregnancy and after birth, revealed genomic instability and mutagenic effects that persisted for 3 years (final year of research). Moraes Filho et al.[25] evaluated that cytotoxicity and genotoxicity of different concentrations of ART composed of tenofovir, lamivudine, and zidovudine, lamivudine, and efavirenz, in mice, through the comet assay and bone marrow micronucleus test. The increase of MN in buccal mucosal cells was observed by Lima et al.[26], in adults with HIV using ART, with low viral load. Our results are in line with the studies identified above that evaluated the effects on rodents and adult individuals.

This study has some limitations. First, it was not possible to evaluate to what extent ART only is able to induce cytogenetic damage in oral cells. Second, the lack of previous research studies on the topic compromise an in-depth discussion regarding the data. Taken together, our results indicate that children infected with HIV and submitted to ART demonstrate genomic damage and cytotoxicity in buccal cells. However, further studies are necessary to elucidate the issue.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The project was approved by the Research Ethics Committee of UNIFESP (Federal University of São Paulo) under protocol number #3.461.911.

AVAILABILITY OF DATA AND MATERIALS

Data sharing are available upon request.

AUTHORS' CONTRIBUTIONS

MESA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **MMC:** Conceptualization, Data curation, Supervision, Writing – original draft. **DVS:** Methodology, Software, Validation, Visualization. **DAR:** Conceptualization, Formal Analysis, Funding acquisition, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **CMCBM:** Data curation, Investigation, Writing – original draft.

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ORIGINAL ARTICLE

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Quality of life for patients with in-stent restenosis after interventional therapy of peripheral artery disease

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the quality of life for patients with in-stent restenosis after interventional therapy of peripheral artery disease and the influencing factors.

METHODS: A total of 72 in-stent restenosis patients after interventional therapy of peripheral artery disease were enrolled, whose general data were obtained. SF-12 scale was used to evaluate the quality of life. Tilburg Frailty Scale was used to assess senile debilitation. Pittsburgh Quality Index Scale was used to evaluate sleep quality. Activity of Daily Living Scale was used to evaluate the self-care ability. The general data and in-stent restenosis-related indicators were compared between patients with low and high quality of life, respectively. Multivariate regression analysis was made on the factors affecting quality of life.

RESULTS: The average total quality of life score of 72 patients was 74.06±19.26 points. The gender, Fontaine stage and smoking, Activity of Daily Living Scale score, painless walking distance, senile debilitation score, sleep quality score, white blood cells, and C-reactive protein had significant differences between the two groups, respectively ($p<0.05$). Multivariate regression analysis showed that the female gender, low Fontaine stage (OR=0.186), low senile debilitation score (OR=0.492), and high sleep quality score (OR=0.633) were the protective factors for high quality of life (all $p<0.05$), and the low Activity of Daily Living score (OR=1.282) was the risk factor for high quality of life ($p<0.05$).

CONCLUSION: Quality of life of in-stent restenosis patients after interventional therapy of peripheral artery disease is low. Gender, Fontaine stage, senile debilitation, sleep quality, and Activity of Daily Living score are the influencing factors of quality of life for in-stent restenosis patients.

KEYWORDS: Quality of life. Constriction. Peripheral artery disease.

INTRODUCTION

Peripheral artery disease (PAD) is a form of arteriosclerosis that occurs in the extremities and involves Ischemia. It is a common disease in vascular surgery. Due to chronic occlusion of peripheral artery, the clinical manifestations of PAD are the pain in lower limb, intermittent claudication, severe limb ulcer, and gangrene, leading to a serious decline in the daily quality of life (QOL)[1]. The incidence of PAD increases exponentially with the increase in age[2]. Interventional treatment has become the preferred surgical treatment method for PAD due to the low incidence of complications, fast postoperative recovery, and short hospitalization time. However, in-stent restenosis (ISR) is a common complication after the lumen stent implantation, which will lead to the recurrence of arterial occlusion symptoms. According to statistics, the rate of ISR within 1 year is as high as 20–50%[3,4], and within 2 years, it is as high as at 60%[5]. As PAD is an incurable chronic progressive disease, mitigating the symptoms of patients and improving the QOL have become the common understanding of more scholars[6]. A previous study has shown that improving the quality of executing functional tasks, such as bathing, stair climbing, and walking, can enhance the QOL of PAD patients[7]. At present, the research on ISR focuses more on risk predictors, prevention, and medical methods through medication and surgery. There is less research on the current QOL, daily living ability, or related influencing factors of ISR patients. Does the QOL of PAD patients decrease or remain unchanged after interventional therapy? This study aimed to investigate the QOL for patients with ISR after interventional therapy of PAD and the influencing factors, for providing a basis for further developing personalized nursing interventions to improve the QOL of PAD patients.

METHODS

Patients

A total of 106 patients with ISR after interventional therapy of PAD in Third Hospital in Hangzhou from January 2016

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to August 2021 were consecutively recruited in this study. The inclusion criteria were as follows: (i) patients who were over 55 years old, (ii) those who met the diagnostic criteria of ISR—vascular restenosis of the lesion segment (stenosis>50% of the target vessel) in PAD patients determined by color ultrasound or occlusion, and (iii) those who required target lesion blood flow reconstruction of target lesions. target lesion blood flow reconstruction was defined as restenosis or occlusion of target blood vessels and repeated symptoms such as affected limb chills, pain, intermittent claudication, and resting pain. Conservative treatment was ineffective, and re-surgical intervention was required. The exclusion criteria were as follows: (i) conservative treatment was effective; (ii) restenosis<50%; (iii) patients with severe cognitive dysfunction or other reasons who cannot communicate; and (iv) other diseases seriously affecting the quality of life, such as intractable heart failure, chronic kidney disease, and respiratory failure. Finally, 34 patients (32.08%, 34/106) were excluded, and 72 patients (67.92%, 72/106) were included. This study was approved by the ethics committee of Hangzhou Third Hospital. Written informed consent was obtained from all participants.

Study methods

The general data of patients were obtained from the medical records within 24 h after they were admitted. The Fontaine classification system was used for staging PAD as follows[8]: Stage I:asymptomatic; Stage II: intermittent claudication; Stage III: rest pain; and Stage IV: necrosis and/or gangrene of the limb. The fasting blood samples were taken in the morning of the first day after admission, and the biochemical indexes were determined using a fully automatic blood analyzer. In addition, within 24 h after admission, SF-12 scale[9] was used to evaluate the QOL of patients, including Physical Component Summary (PCS) Scale and Mental Component Summary (MCS) Scale. Tilburg Frailty Scale was used to assess the senile debilitation of patients[10]. Pittsburgh Quality Index Scale (PSQI)[11] was used to evaluate the sleep quality of patients. Activity of Daily Living Scale (ADL) was used to evaluate the self-care ability of patients[12]. The data of the questionnaire survey were collected by a senior nurse who was familiar with the contents.

Statistical analysis

Data were statistically analyzed using the SPSS 22.0 software. Measurement data of normal distribution were described by mean±standard deviation and were compared using the independent-sample t-test. Non-normal distributed measurement data were described by M (P_{25}–P_{75}), and the groups were compared by the Mann-Whitney test. Classification data were described by frequency (percentage), and the Pearson χ^2 test was used for comparison between groups. Multivariate logistic regression was used to study independent factors affecting patient QOL. $p<0.05$ was considered significantly different.

RESULTS

Quality of life scores of patients

The questionnaire with SF-12 scale showed that the lowest, highest, and average PCS scores of 72 ISR patients were 20.24, 54.84, and 35.97±10.14 points, respectively, and the lowest, highest, and average MCS scores were 19.37, 59.78, and 38.09±10.53 points, respectively. The lowest, highest, and average total QOL scores (PCS+MCS) were 46.95, 114.61, and 74.06±19.26 points, respectively.

Comparison of general data between patients with low and high quality of life

Based on the median of total QOL scores, 72 ISR patients were divided into low QOL group (n=36) and high QOL group (n=36). The gender, Fontaine stage, and smoking status had significant difference between the two groups, respectively ($p<0.05$). There was no significant difference in other general data between the two groups ($p>0.05$) (Table 1).

Comparison of in-stent restenosis-related indicators between patients with low and high quality of life

As shown in Table 2, the ADL score, painless walking distance, senile debilitation score, sleep quality score, white blood cells, and C-reactive protein had significant difference between the low and high QOL groups, respectively ($p<0.05$). There was no significant difference in ISR-related indicators between the two groups ($p>0.05$).

Multivariate regression analysis results of factors influencing quality of life

Using QOL as the dependent variable and gender, Fontaine stage, smoking, ADL score, painless walking distance, senile debilitation score, sleep quality score, white blood cells, and C-reactive protein as regression variables, the multivariate regression analysis was performed. Results showed that the female gender, low Fontaine stage, low senile debilitation score, and high sleep quality score were the protective factors for high QOL. The low ADL score was the risk factor for high QOL (Table 3).

Table 1. Comparison of general data between in-stent restenosis patients with low and high quality of life after interventional therapy of peripheral artery disease.

Index	Low QOL	High QOL	t/χ^2	p
n	36	36		
Age (age)	77.06±7.18	73.86±7.51	1.844	0.069
BMI (kg/m^2)	22.11±3.59	22.53±3.26	0.516	0.608
Gender, n (%)			6.923	0.009
Male	31 (86.1)	21 (58.3)		
Female	5 (13.9)	15 (41.7)		
Education, n (%)			0.441	0.932
Illiterate	12 (33.3)	10 (27.8)		
Primary school	14 (38.9)	14 (38.9)		
Junior high school	8 (22.2)	9 (25.0)		
Senior high schools and above	2 (5.6)	3 (8.3)		
Smoking status, n (%)	28 (77.8)	14 (38.9)	11.200	0.001
Disease history, n (%)				
Hypertension	30 (83.3)	25 (69.4)	1.925	0.165
Diabetes	19 (52.8)	13 (36.1)	2.025	0.155
Cerebral infarction	15 (41.7)	8 (22.2)	3.130	0.077
Coronary heart disease	7 (19.4)	5 (13.9)	0.400	0.527
Affected limb, n (%)			0.229	0.633
Left lower limb	14 (38.9)	16 (44.4)		
Right lower limb	22 (61.1)	20 (55.6)		
Fontaine stage, n (%)			9.864	0.007
II	5 (13.9)	15 (41.7)		
III	7 (19.4)	1 (2.8)		
IV	24 (66.7)	20 (55.6)		
Use of antiplatelet or vasodilator drugs, n(%)	27 (75.0)	27 (75.0)	0.000	1.000

ISR: in-stent restenosis; QOL: quality of life; PAD: peripheral artery disease; BMI: body mass index.

DISCUSSION

This study has investigated the QOL for patients with ISR after interventional therapy of PAD and the influencing factors. It is indicated that the QOL of ISR patients after interventional therapy of PAD is low. Gender, Fontaine stage, senile debilitation, sleep quality, and ADL score are the influencing factors of QOL for ISR patients.

In this study, the average total QOL score of patients with ISR was at a lower middle level. This is similar to the study results by Wu et al.[13] The vascular occlusion symptoms occur after intervention treatment of PAD, including intermittent lameness, resting pain, and foot gangrene symptoms, leading to different degrees of lower limb pain and difficult-to-heal foot ulcer. The patients cannot walk, climb stairs, dress, go toilet, or even complete other daily activities. In addition, the occurrence of ISR not only makes the patient feel physical pain but also increases the negative psychological mood and reduces happiness. Depression is a common negative psychological mood in patients with arterial disease[14]. Resting pain leads to poor sleep at night, causing anxiety, fear, and other bad emotions[15]. These can cause the low QOL of ISR patients.

Fontaine stage is based on the clinical symptoms of PAD patients. It is reported that the lower QOL is related to the higher Fontaine stage[16]. This is consistent with the findings of our study in which the low Fontaine stage is a protective factor for high QOL. A previous study[17] has shown that decreased ADL score severely affects the QOL of the elderly. This is consistent with the findings of our study in which the

Table 2. Comparison of in-stent restenosis-related indicators between patients with low and high quality of life after interventional therapy of peripheral artery disease.

ISR-related indicator	Low QOL	High QOL	t/z	p
n	36	36		
Time before reoccurrence (months)	18.94±17.05	14.14±10.50	1.440	0.155
Time before visiting (days)	30 (15–90)	20 (14–50)	1.663	0.096
NRS pain score (points)	3.08±2.06	2.39±1.27	1.720	0.090
ADL score (points)	68.75±12.89	95.00±6.09	3.487	0.000
Painless walking distance (m)	45 (10–100)	100 (50–300)	3.159	0.003
Senile debilitation score (points)	8.19±1.83	4.89±2.29	6.761	0.000
Sleep quality score (points)	12.39±4.08	7.75±3.83	4.971	0.000
Type of drugs (n)	4.78±2.84	3.92±2.44	1.379	0.172
Biochemical indexes				
Triglyceride (mmol/L)	1.46±1.54	1.33±1.04	0.430	0.669
LDL (mmol/L)	2.30±1.11	2.74±1.21	1.608	0.112
HDL (mmol/L)	1.18±0.38	1.20±0.39	0.306	0.761
Albumin (g/L)	33.67±4.28	34.93±3.44	1.380	0.172
Apolipoprotein A1 (g/L)	1.27±0.30	1.30±0.31	0.293	0.771
Apolipoprotein B (g/L)	0.75±0.34	0.88±0.39	1.475	0.145
Total protein (g/L)	62.78±5.07	60.79±6.32	1.471	0.146
Total cholesterol (mmol/L)	3.88±1.27	4.66±3.22	1.340	0.185
White blood cells (10^9/L)	6.9 (5.7–9.43)	5.95 (5.3–6.8)	2.091	0.037
Blood platelet (10^9/L)	227.36±105.93	229.92±81.72	0.115	0.909
C-reactive protein (mg/L)	3.95 (1.2–33.18)	1.45 (0.63–5.78)	2.198	0.028
Mean platelet volume (fL)	10.70±1.09	10.27±1.04	1.736	0.087

ISR: in-stent restenosis; QOL: quality of life; PAD: peripheral artery disease; NRS: Numerical Rating Scale; ADL: Activity of Daily Living Scale; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 3. Multivariate regression analysis results of factors influencing quality of life of in-stent restenosis patients after interventional therapy of peripheral artery disease.

Factor	B	SE	Wald	p	OR	95%CI
Gender	-4.064	2.075	3.835	0.048	0.017	0.001–0.903
Fontaine stage	-1.682	0.865	3.981	0.042	0.186	0.034–0.914
Senile debilitation score	-0.709	0.360	3.871	0.049	0.492	0.243–0.997
Sleep quality score	-0.458	0.197	5.375	0.020	0.633	0.430–0.932
ADL score	0.248	0.086	8.234	0.004	1.282	1.082–1.518

QOL: quality of life; ISR: in-stent restenosis; PAD: peripheral artery disease; ADL: Activity of Daily Living Scale; B: regression coefficient; SE: standard error; Wald: corresponding to χ^2 value; p: difference; OR: odds ratio; CI: confidence interval.

ADL score is low in the low QOL group. In addition, the logistic regression analysis showed that patients with ADL scores had poor QOL. These indicate that patients with low QOL are in a state of slight dependence and need care from others in their daily life.

Senile debilitation is an elderly syndrome affecting multiple functional domains in humans and shares the same pathogenesis and risk factors as PAD[18]. Our study showed that senile debilitation is a risk factor for decreased QOL in ISR patients. Exercise is an effective way to prevent and

treat weakness. Therefore, we can improve the QOL of ISR patients by guiding them to adhere to exercise. It is believed that the elderly themselves are prone to various sleep disorder symptoms, which seriously affects the QOL[19]. Our study finds that a high sleep quality score is one of the protective factors for high QOL. Therefore, the nurses should assess the cause of poor sleep of ISR patients and take targeted care measures. In addition, our study shows that female gender is one of the protective factors for high QOL, which is different from a foreign study[20], which may be related to the race of research objects.

Our study still has some limitations. First, this study conducted a single-center research, with a small sample size. The next multi-center and large-sample size investigation should be performed for obtaining more persuasive findings. Second, there were obviously more male patients than female patients in this study. If more female patients participate in the study, we may rule out different results. In the future study, more female patients should be enrolled to make the findings more convincing.

CONCLUSION

QOL of ISR patients after interventional therapy of PAD is low. Gender, Fontaine stage, senile debilitation, sleep quality, and ADL score are the influencing factors of QOL for ISR patients. Therefore, delaying the recurrence of ischemic symptoms, mitigating the debilitation, improving the activities, and ensuring good sleep quality are the keys to improve the QOL of ISR patients.

AUTHORS' CONTRIBUTIONS

JT: Conceptualization, Formal Analysis, Investigation, Project administration, Resources, Supervision, Writing – review & editing. **ZZ:** Data curation, Funding acquisition, Software, Writing – original draft. **FX:** Validation, Visualization. **LL:** Methodology, Validation, Visualization.

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ORIGINAL ARTICLE

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Evaluation of patients via colonoscopy who underwent positron emission tomography/computerized tomography due to colon involvement

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SUMMARY

OBJECTIVE: Fluorodeoxyglucose is not a tumor-specific agent and it can also be involved in benign conditions, which may cause diagnostic confusion. This research aims to elucidate the colonoscopic findings of patients who underwent colonoscopy due to colon involvement in positron emission tomography/computerized tomography.

METHODS: A total of 71 patients who underwent colonoscopy due to colonic involvement in positron emission tomography/computerized tomography at SBU Keçiören Training and Research Hospital Gastroenterology Clinic Endoscopy Unit have been analyzed retrospectively. Demographic characteristics of the patients, areas of involvement in positron emission tomography/computerized tomography, and severity have been obtained from the hospital database.

RESULTS: The gastrointestinal involvement area of 22.5% (n=16) of the patients was ascending colon, 15.5% (n=11) was sigmoid, 15.5% (n=11) was rectum, 12.7% (n=9) was stomach, 11.3% (n=8) was transverse colon, 8.5% (n=6) was anal canal, 5.6% (n=4) was esophagus, and 5.6% (n=4) was descending colon. The endoscopic findings of 19.7% (n=14) patients were normal, whereas 29.6% (n=21) had polyps, 9.9% (n=7) had cancer, 2.8% (n=2) had an ulcer, 15.5% (n=11) had gastritis, 14.1% (n=10) had hemorrhoids, and 7% (n=5) had colitis.

CONCLUSION: Fluorodeoxyglucose-positron emission tomography can detect unexpected distant metastases with high sensitivity because it allows whole-body imaging. Curative resection significantly contributes to the choice of treatment modality in the pre-operative period of colorectal cancer patients with planned surgery.

KEYWORDS: PET-CT. Colorectal cancer. Colonoscopy. Metastasis.

INTRODUCTION

Colorectal cancers (CRCs) are the third most common cancer among newly diagnosed cancer patients[1]. Liver metastases are detected in approximately half of the CRC patients within the first 5 years after diagnosis. Rectal cancers constitute approximately one-third of all CRCs, with metastatic disease observed in approximately one-quarter of cases at diagnosis[2].

Accurate and complete staging is essential for effective treatment. Contrast-enhanced computerized tomography (CT) is frequently used in staging CRCs but it has limitations[3]. These limitations pave the way for fluorodeoxyglucose (FDG) positron emission tomography (PET/CT), a functional imaging method that can provide helpful pre-operative staging and follow-up information. A multimodality approach is recommended for evaluating treatment response because no guideline recommends the ideal method to evaluate the treatment response[4].

Imaging methods are crucial in evaluating the localization, borders, and spread of CRC, but no imaging format can meet all diagnostic expectations[5]. Anatomical techniques such as ultrasonography, CT, and MRI are used to detect metastases. Still, PET/CT has been widely used in recent years due to its non-invasive nature and ability to diagnose stage and follow-up treatment response[6]. Also, FDG-PET allows whole-body imaging in a single session and can detect relapse and metastatic disease with high accuracy. However, FDG is not a tumor-specific agent and may cause diagnostic confusion[7]. This research aims to elucidate the colonoscopic findings of patients who underwent colonoscopy due to colon involvement in PET-CT.

METHODS

We analyzed 71 patients who underwent colonoscopy from colonic involvement in PET/CT at SBU Keçiören Training and Research Hospital Gastroenterology Clinic Endoscopy Unit between January 2016 and December 2018. Ethical standards were followed according to Declaration of Helsinki 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 2012–KAEK–15/23179, and informed consent was obtained.

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Demographic characteristics of the patients (age, gender, and comorbidity), areas of involvement in PET-CT, and severity were recorded.

In patients with pathologically confirmed lung cancer, PET-CT was performed for staging purposes, and patients with an SUV_{max} value of 2.5 and above in the gastrointestinal tract (GIS) were evaluated. TNM staging system is used in the cases of gastrointestinal system involvement. Stage 0: Cancer is at the earliest possible stage. At this stage, the disease is also called in situ or intramucosal carcinoma (*Tis*). Cancer cells are found only in the mucous layer, which is the innermost wall layer of the colon or rectum. Stage 1: Cancer cells have reached the submucosa from the mucosa to a lower layer (T1) or the underlying muscle layer (T2). No regional lymph nodes or distant metastases (N0 and M0). Stage 2A: Cancer has reached the outermost layer of the colon or rectum wall but has not exceeded it (T3) and has not spread to surrounding organs. There are no regional lymph nodes or distant metastases (N0 and M0). Stage 2B: Cancer has invaded all colon or rectum wall layers, but has not spread to surrounding organs or tissues (T4a). There is no distant metastasis in regional lymph nodes or distant metastases yet (N0 and M0). Stage 2C: Cancer has spread beyond the colon or rectum wall and has adhered to or grown into the surrounding organs or tissues (T4b). There are no distant metastases in the regional lymph nodes or distant metastases yet (N0 and M0). Stage 3A: Cancer cells have reached the submucosa (T1) or the underlying muscle layer (T2) from the mucosa. The regional lymph nodes (1–3) are involved (N1a/N1b), or there is tumor not in the lymph nodes but in the adipose tissue close to the lymph nodes (N1c). There is no distant metastasis (M0). Stage 3B: Cancer has reached the outermost layer of the colon or rectum wall (T3) or has involved all layers of the colon or rectum wall (T4a) but has not spread to the surrounding tissues and organs. The regional lymph nodes (1–3) are involved. Stage 4: Regardless of T and N stages, cancer can reach one distant organ (e.g., liver or lung) or has metastasized to distant lymph nodes (M1a).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software. Descriptive statistics, t-tests, Mann-Whitney U tests, and correlation analyses were performed with a 95% confidence interval and p-value of <0.05 as statistically significant. In comparing variables according to gender groups, the Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables.

RESULTS

This study observed 71 patients who had colonoscopies due to colonic involvement. Most patients (78.9%) were males and the average age was 68.52 years. There were no significant age differences between male and female patients. No statistically significant difference has been observed between the mean ages by gender.

Male patients had a mean thorax SUV_{max} of 10.15±6.38 (IQR 0–24.52), while female patients had a mean of 9.16±8.46 (IQR 0–27.2). There were no significant differences in SUV_{max} values between genders. Details are shown in Table 1.

Of the 71 patients who underwent PET/CT, 66.2% (n=47) had lung cancer, 16.9% (n=12) had nodules, 8.5% (n=6) had infiltration, and 4.2% (n=3) had other cancer types. Male patients were more likely to have lung cancer than female patients [71.4% (n=40)].

PET stages varied among the patients, with 26.8% (n=19) having stage 0 and 28.2% (n=20) having stage 4. The gastrointestinal involvement area of 22.5% (n=16) of the patients was ascending colon, 15.5% (n=11) was sigmoid, 15.5% (n=11) was rectum, 12.7% (n=9) was stomach, 11.3% (n=8) was transverse colon, 8.5% (n=6) was anal canal, 5.6% (n=4) was esophagus, and 5.6% (n=4) was descending colon (Table 2).

Notably, 22.5% (n=16) of patients had involvement in the ascending colon, 15.5% (n=11) in the sigmoid, and 15.5% (n=11) in the rectum. Most of them had focal involvement (81.7%) and diffuse involvement was observed in 18.3%.

Table 1. Analyses of gastrointestinal tract SUV_{max} averages by gender.

Continuous variables and gender		n	Mean	SD	Minimum	Maximum	Median	p-value	t	u
Age (years)	Male	56	67.93	8.805	53	85	68.5	0.326	-0.99	
	Female	15	70.73	12.775	43	92	72			
Primary thorax mass SUV_{max} value	Male	56	10.155	6.38	0	24.52	10	0.569	0.572	
	Female	15	9.16	8.46	0	27.2	5.32			
GIS SUV_{max} value	Male	56	10.025	6	2.78	35	8.04	0.811		403
	Female	15	10.25	5.96	3	24	8.65			

In comparing variables according to gender groups, the Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. GIS: gastrointestinal tract, SD: standard deviation.

Endoscopic findings showed normal results for 19.7% (n=14), polyps for 29.6% (n=21), and cancer for 9.9% (n=7). Adenomatous polyps were found in only 5.6% (n=4) of patients, whereas hyper polyps were detected in 4.2% (n=3).

Endoscopic findings varied by PET stages, with PET stage 0 showing a significant difference (p=0.017). GIS uptake rates were not statistically different (p=1.00). Details are shown in Table 3.

As a result of ROC analysis (Table 4), it has been observed that the GIS SUV_{max} value did not predict lung cancer (AUC: 0.632, 95%CI: 0.457–0.747, p=0.162). However, the lung mass SUV_{max} variable was important in predicting lung cancer (AUC: 0.916, 95%CI: 0.844–0.988, p<0.001).

Table 2. Localization of gastrointestinal system involvement.

		Frequency	%
GIS Involvement	Anal canal	6	8.5
	Esophagus	4	5.6
	Stomach	9	12.7
	Cecum	2	2.8
	Ascending colon	16	22.5
	Transverse colon	8	11.3
	Descending colon	4	5.6
	Sigmoid	11	15.5
	Rectum	11	15.5
	Total	71	100.0

DISCUSSION

FDG PET/CT is a powerful imaging tool used for tumor imaging, staging, and follow-up, providing valuable data on both primary indications and incidental findings. Incidental FDG uptake was found in 3.6% of patients in PET/CT evaluations for non-GI system diseases[8]. However, false positive involvements were detected in 9.3–63% of patients, emphasizing the need to interpret PET/CT results[9] carefully.

Rigault et al. detected at least one lesion on colonoscopy in 46% out of 70% of patients with incidental focal colorectal FDG uptake[10]. Putora et al. identified colonoscopic lesions in 44 out of 51 patients with colonic involvement[11].

Many tests (colonoscopy, whole abdomen CT, thorax CT, endoscopic ultrasonography, and bone scintigraphy) should be performed together to evaluate the whole body for metastasis with conventional methods[12]. FDG-PET imaging evaluates the whole body for metastasis in a single session without additional radiation exposure. This is particularly useful for patients with advanced or recurrent diseases who require frequent monitoring. Studies have shown that FDG-PET detected all extrahepatic metastases with 100% sensitivity[13].

Table 3. Combined positron emission tomography stage and combined endoscopic finding cross-table analysis.

PET stage and GIS involvement			GIS attendance location		Total
			Esophagus, stomach, and duodenum	Cecum, ascending colon, transverse colon, descending colon, sigmoid, rectum, anal canal	
PET stage	0	n	3	16	19
		%	15.8%	84.2%	100.0%
	1- 1A-1B-2-2A-2B	n	3	14	17
		%	17.6%	82.4%	100.0%
	3A-3B-4	n	7	28	35
		%	20.0%	80.0%	100.0%
Total		n	13	58	71
		%	18.3%	81.7%	100.0%

p=1.00 and Fisher's test=0.201.

Table 4. Positron emission tomography computerized tomography SUV_{max} ROC analysis.

	AUC	p-value	Sensitivity %	Specificity %	Cutoff value	95%CI	Positive predictive value %	Negative predictive value %
Lung main mass SUV_{max}	0.916	**0.000**	0.723	0.958	9.575	0.844–0.988	97.1	63.9
GIS SUV_{max}	0.602	**0.162**	0.66	0.667	0.765	0.457–0.747	79.5	50

According to the ROC analysis, it was observed that the GIS SUVmax value did not predict lung cancer (p-value=0.162). However, the SUVmax value of the primary lung mass was significant in predicting lung cancer. The p-value was 0.000.

PET/CT is a non-invasive technique used to determine diagnosis, staging, and response to treatment, demonstrates tumor aggressiveness, and determines radiotherapy areas. In addition, PET/CT examination can detect focal or nodular hypermetabolic lesions in the GIS with a high probability of pre-malignant/malignant lesions. Therefore, colonoscopic evaluation is recommended for these lesions[14].

In a study conducted by Hu et al. consisting of 149 patients diagnosed with cancers without a definite primary focus, FDG uptake consistent with malignancy was found in 50 patients (33.6%) with PET/CT, and in 37 patients (24.8%) with PET/CT and histopathological examination. As a result of the study, the sensitivity and specificity were determined as 86% and 87.7% with PET/CT[15]. In a study by Fencl et al. on 190 patients, the rate of detecting a primary focus was 47%, the sensitivity was 94%, and the specificity was 86%[16]. Pelosi et al. reported that PET/CT could reveal the primary focus in 35.2% of patients in their study who were proven to have metastatic carcinoma with 39 lymph nodes and 29 visceral biopsies. This study determined the positive predictive value (PPD) as 82%[17]. In this study, we found that GIS uptake rates were not statistically different according to PET stages (p=1.00, Fisher's test=0.201).

Kwee and Kwee have conducted a meta-analysis of 11 studies on 433 patients and found the range of primary tumor detection to be 22–73% by PET/CT. According to this meta-analysis, the lungs were the organs in which primary tumors were detected the most at 33%, followed by oropharyngeal cancers at 16%, and pancreatic cancers at 5%[18].

Colonic FDG uptake in PET-CT was frequently associated with neoplastic pathology in different publications. In a different study, 10,978 patients were evaluated, and colonic FDG uptake was detected in 148 patients. Colorectal tumors were found in 23.5% of the cases, polyps in 20.5%, and normal findings in 56%. It has also been reported that the false positive rate of focal FDG uptake, especially in the right colon, is high[19].

In a study comparing colonoscopy and PET/CT findings simultaneously of 123 polyps with focal involvement, 9 were adenocarcinoma and 6 were high-grade dysplasia. Regarding this, one could state that in polyps larger than 10 mm, FDG uptake was found to be less homogeneous in adenomas (>10 mm) than in adenocarcinomas (>10 mm)[20].

In FDG PET/CT studies, primary CRCs were detected as small as 14 mm with high FDG uptake[21]. The diameter of the undetected polyps was 13 mm and had the character of adenoma. It was found that the positivity of PET increased (90%) with the enlargement of the adenoma size (>13 mm)[22]. In another study, the sensitivity of FDG-PET was also determined by the enlargement of the adenoma (1–5 mm 21%, 6–10 mm 47%, and >11 mm 72%) and the degree of dysplasia (low-grade dysplasia 33%, high-grade dysplasia 76%, and carcinoma 89%) increased[23].

In a different study, when compared with colonoscopy, the sensitivity of PET/CT was 74%, specificity was 84%, and PPD was 78%. Again, a good correlation was found between FDG uptake and the localization of endoscopy-positive lesions, supporting the usefulness of FDG PET/CT in the non-invasive follow-up of patients with CRC and the detection of other colonic lesions. In addition, the FDG uptake was proportional to the degree of dysplasia in the adenoma[24]. However, it should not be forgotten that FDG accumulates in areas of inflammation or infection in whole-body scans of cancer patients. This causes a decrease in specificity in body scanning, as the infection may mimic metastasis[25]. In this study, the rates of endoscopic findings were statistically different according to PET stages, and the difference was due to the PET stage 0 group (p=0.017).

CONCLUSION

FDG-PET can detect unexpected distant metastases with high sensitivity because it allows whole-body imaging. PET, which has become increasingly used with the advantage of being non-invasive in cancer staging and surveillance, can detect mostly adenomatous polyps incidentally. Curative resection significantly contributes to the choice of treatment modality in the pre-operative period in patients with CRCs with the planned surgery.

INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with Declaration of Helsinki 1975, as revised in 2008. Informed consent was obtained from all participants.

INSTITUTIONAL REVIEW BOARD APPROVAL

This study has been approved by the ethics committee with protocol number *2012–KAEK–15/23179.*

AUTHORS' CONTRIBUTIONS

MÖE: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing. **EKA:** Data curation, Formal Analysis, Funding acquisition, Project administration, Software, Validation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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The effect of Pilates on pain during pregnancy and labor: a systematic review and meta-analysis

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SUMMARY

OBJECTIVE: This systematic review and meta-analysis study was conducted to reveal the effect of Pilates on pain during pregnancy and labor.
METHODS: The PubMed, ScienceDirect, MEDLINE, Ovid, EBSCO, CINAHL Plus, Cochrane Library databases, and Google Scholar databases were used to access the articles published in international journals, and the Dergipark, Turkish Clinics, and ULAKBİM databases were scanned to access the articles published in national journals between October 30 and November 30, 2022. The data were analyzed using Review Manager 5.4.
RESULTS: This study included four articles. According to the meta-analysis results, it was elucidated that Pilates exercise during pregnancy was not statistically effective in reducing pain during pregnancy (Z=0.61, p=0.54), but it was effective in reducing pain intensity during labor (Z=11.20, p<0.00001).
CONCLUSION: This study concluded that Pilates exercise was not effective in reducing pain during pregnancy but was effective in reducing labor pain. There is a need for more research on the subject.
PROSPERO Registration no: CRD42023387512
KEYWORDS: Obstetric labor. Pregnancy. Exercise. Meta-analysis. Pain.

INTRODUCTION

Pilates is mainly a mind-body exercise done for muscle strength, flexibility, breathing, and posture. It concentrates on actively using the trunk muscles to stabilize the pelvic-lumbar region[1,2]. Regular Pilates exercise has been shown to strengthen the transverse abdominal and pelvic floor muscles and enhance their structural function. Moreover, Pilates is considered an exercise of low-to-moderate intensity to relieve pain[3]. It ensures flexibility, dynamic balance, and muscle endurance in healthy populations. It positively affects back pain, quality of life, balance, and physical and mood states[4].

As a result of postural changes caused by weakness of joints and ligaments and muscle-tendinous stretching during pregnancy, pregnancy-related musculoskeletal problems may arise[1,2,5]. Furthermore, pregnancy-related musculoskeletal problems can be affected by the degree of physical activity, cultural influences, and environmental and hormonal changes. Relaxin, a hormone secreted by the placenta, especially in the late stages of pregnancy, loosens the ligaments in the pelvis for the labor process. Meanwhile, it triggers pregnancy-related pain by loosening the ligaments that support the spine[1,2]. Pain is seen especially in the back, lumbar, pelvic, and extremity regions[1,6-8]. Pain, which significantly affects the daily lives, mobility, and sleep of pregnant women and reduces their quality of life substantially, can reach quite serious dimensions with the progression of pregnancy[9,10]. Pilates movements can be performed according to the physiological changes during pregnancy to overcome musculoskeletal problems[3,7]. Pilates exercise during pregnancy prepares a woman for labor. Improving the flexibility of the trunk and pelvic floor muscles and ensuring correct breathing can facilitate the labor process[3]. Moreover, Pilates has been shown to reduce labor pain[3,11].

It is assumed that the pain suffered during pregnancy and labor will decrease with correctly performing muscle strengthening and breathing, which is the basis of Pilates. When the effectiveness of the method is determined, it may be recommended to be used more often to reduce low back pain in pregnant women and labor pain. This systematic review and meta-analysis study was conducted to reveal the effect of Pilates exercise on pain during pregnancy and labor.

Research questions

- What is the effect of Pilates exercise on pain during pregnancy?
- What is the effect of Pilates exercise on labor pain?

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METHODS

A systematic review and meta-analysis study was conducted to reveal the effect of Pilates on pain during pregnancy and labor. The primary outcome of this study was the level of pain during pregnancy and labor, which was measured by a valid and reliable tool. The secondary outcome was an adverse event, which was also measured by a valid and reliable tool. In the preparation of systematic review and meta-analysis, the criteria from PRISMA[12] and the Cochrane Experiments Systematic Reviews Handbook were used. Prior to the study, the subject of the study and whether it was among the previously completed or ongoing studies were checked from the PROSPERO system.

The review of the articles included, the selection of the articles, the acquisition of the data, and the quality assessment were conducted independently by the first and second researchers, and all stages were checked by the third and fourth researchers. In case of any disagreement about the study, a meeting was held in which four researchers participated together, disagreements were discussed, and a consensus was reached. Moreover, a pilot study was conducted, and a common road map was determined regarding all these stages in a session with the participation of four researchers before initiating the study.

Criteria for including studies in the review

Inclusion and exclusion criteria were set considering the components of the research problem (PICOS). Accordingly,

Population (P); Pregnant women

Intervention (I); Pilates

Comparison (C); Women who did not do Pilates during pregnancy

Outcomes (O); Pain

Study design (S); Randomized controlled trials published in Turkish and English between 1984 and 2022.

Quasi-experimental studies, reviews, case reports, qualitative studies, unpublished theses, congress papers, and descriptive studies constituted the exclusion criteria of the study.

Review strategy

This systematic review and meta-analysis study was conducted between October 30 and November 30, 2022, in the form of a retrospective review of publications on the subject. The PubMed, ScienceDirect, MEDLINE, Ovid, EBSCO, CINAHL Plus, Cochrane Library databases, and Google Scholar databases were used to access the articles published in international journals, and the Dergipark, Turkish Clinics, and ULAKBİM databases were scanned to access the articles published in national journals. The search was done in Turkish and English over Istanbul University-Cerrahpaşa Internet access network using keywords such as (pregnancy OR antenatal period OR labor OR birth) and (women OR pregnant women OR pregnancy) AND (Pilates) and (pain OR low back pain OR labor pain). Furthermore, the reference lists of the studies included in the study were reviewed to identify additional studies.

Selection of studies

Studies to be included in this study were determined and selected independently by two researchers, considering the inclusion and exclusion criteria. The titles and abstracts of all studies were reviewed. The articles selected independently by the first and second authors were compared. In case of different views on articles, a joint decision was made by considering the views of the third and fourth authors.

Acquisition of study data

A data extraction form was created by the researchers to obtain the same information from each study included in the systematic review. The data extraction form included information about the author, year of the study, country, type of study, sample size, data collection tools, mean age of the pregnant women included in the study, data on the intervention, and information about pain.

Evaluation of the evidence quality of studies

Each study selected to be included in the study was assessed by the first two authors with a critical appraisal checklist and checked by the third and fourth authors. The quality of the articles in randomized controlled trials was assessed via the Second Version of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2)[13].

Data analysis

In the meta-analysis, data analysis was performed using Review Manager 5.4 (The Nordic Cochrane Center, Copenhagen, Denmark). The heterogeneity between the studies reviewed was assessed by Cochran's Q and Higgins' I^2 tests, and it was accepted that I^2 higher than 50% indicated a significant heterogeneity. Accordingly, the Random Effect result was obtained if I^2 was higher than 50%, and the Fix Effect result was obtained if it was <50%. To evaluate the study data, Standardized Mean Difference (SMD) and Mean Difference (MD) were used for continuous variables. All tests were calculated as two-tailed, and $p<0.05$ was accepted for statistical significance.

RESULTS

Review findings

As a result of the literature review, 293 studies were reached at the first stage. As a result of excluding duplicate records and the literature that met the exclusion criteria and analyzing the titles and abstracts, 29 articles were selected for full-text review. After reviewing the full texts according to the inclusion criteria and adding other studies, four studies were determined for meta-analysis: two for pain during pregnancy and two for pain during labor. The primary outcome of this study was the level of pain during pregnancy and labor. There were no studies reporting adverse effects for secondary outcome. Figure 1 shows the PRISMA flowchart for the selection process of the studies.

Quality assessment results of studies

The articles included in the study were assessed with the RoB 2 tool. While no high level of bias was observed in the studies, some concerns about bias were seen in one study, and a low risk of bias was observed in the other three studies (Table 1).

Characteristics of the studies

The total sample size of the studies included in the systematic review and meta-analysis is 204. All the studies included in this research were randomized controlled trials and published in English language (Table 1).

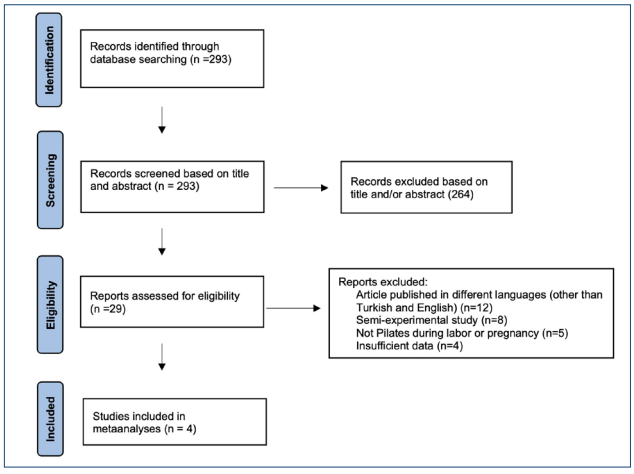


Figure 1. PRISMA flowchart.

Table 1. Characteristics of the studies.

Reference Country	Study design	Study period	Data collection tools	Age Mean±SD	Sample size	Intervention	Pain score	Risk of bias domains: ROB-2
Aktan et al., 2021 Turkey[11]	RCT	N/A	VAS	Pilates: 27.52±3.88 Control: 25.5±4.19	Pilates: 21 Control: 22	16–24 weeks of pregnancy For 8 weeks Twice a week 60 min	Pilates: 6.7±1.19 Control: 8.4±0.79	Some concerns
Ghandali, 2021 Iranian[3]	RCT	2020	VAS	Pilates: 25.16±4.41 Control: 23.81±4.30	Pilates: 51 Control: 52	26–28 weeks of pregnancy For 8 weeks Twice a week 35 min	First measurement Pilates: 5.04±0.99 Control: 6.14±1.07 Second measurement Pilates: 6.20±0.87 Control: 7.46±1.16 Third measurement Pilates: 7.44±0.81 Control: 8.51±1.14	Low risk
Mazzarino et al., 2022 Australia[14]	RCT	N/A	PMI	N/A	Pilates: 11 Control: 7	From the 18th week For 6 weeks At least 30 min	Pilates: 86.4±17.2 Control: 78.6±22.5	Low risk
Sonmezer et al., 2021 Turkey[2]	RCT	2019	VAS	Pilates: 29.00±2.75 Control: 28.00±2.10	Pilates: 20 Control: 20	From 22nd to 24th week For 8 weeks Twice a week 60–70 min	Pilates: 17.20±10.80 Control: 38.40±17.50	Low risk

RCT: randomized controlled trial; VAS: Visual Analog Scale; PMI: Pregnancy Mobility Index; N/A: not applicable; SD: standard deviation.

Characteristics of the intervention

The time of starting Pilates exercise differed in the studies. In the studies, Pilates practice during pregnancy was performed in the second and third trimesters, and in three-quarters of the studies, it was performed as two sessions per week for 8 weeks[2,3,11]. In the studies, the duration of pregnant women's Pilates exercise differed between 30 and 70 min[2,3,11,14] (Table 1).

Meta-analysis findings

The Visual Analog Scale (VAS) was used for pain evaluation in three studies included in the meta-analysis[2,3,11], and the Pregnancy Mobility Index (PMI)[14] was used in one study (Table 1).

The effect of Pilates during pregnancy on pain during pregnancy

Two studies reviewed in this study included data on pain levels in pregnant women who did and did not do Pilates during pregnancy[2,14]. According to the combined results of these studies, it was seen that Pilates exercise during pregnancy was not statistically effective in reducing pain during pregnancy (SMD: -0.55, Z=0.61, p=0.54) (Figure 2).

The effect of Pilates during pregnancy on labor pain

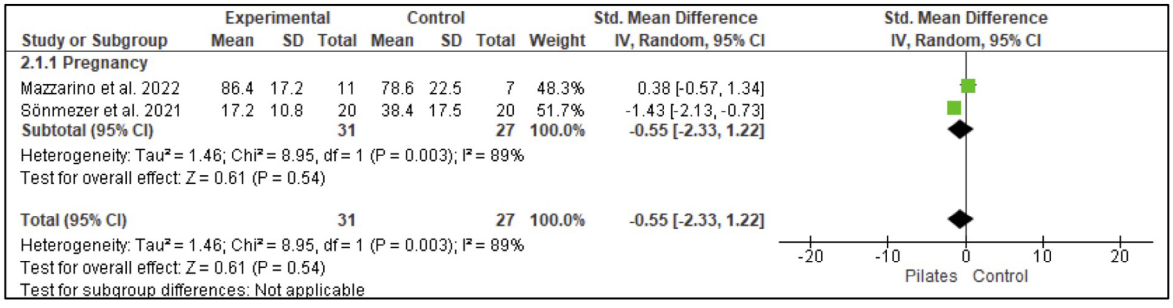
Two studies reviewed in this study included data on labor pain in pregnant women who did and did not do Pilates during pregnancy[3,11]. According to the combined results of these studies, Pilates exercise during pregnancy was found to statistically significantly reduce pain intensity during labor (MD: -1.21, Z=11.20, p<0.00001) (Figure 2).

DISCUSSION

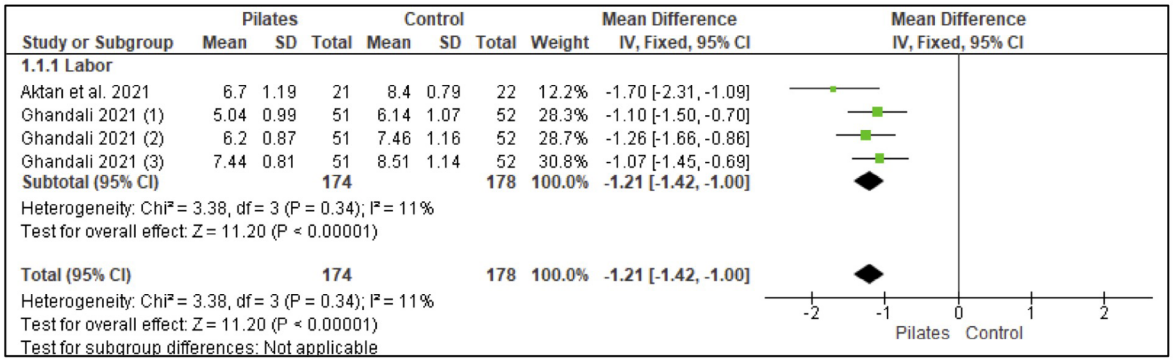
This systematic review and meta-analysis study analyzed the effect of Pilates exercise on pain during pregnancy and labor.

Pregnancy and labor are among the important and special periods experienced by women in their lives. Many changes considered normal may occur during these periods. However, these changes may lead to pain during pregnancy and labor[15,16].

Musculoskeletal system pain may be experienced during pregnancy, affecting the lower back, pelvic region, back, hip, and even wrists. As pregnancy progresses, a decrease is observed in the strength of the pelvic floor muscles and abdominal



Mean = mean of the groups; SD = standard deviation; Weight = statistical relevance of the study; IV = inverse variance; CI = confidence interval; Random = random effect; I^2 = heterogeneity index; Z = global effect test; Chi^2 = Chi-square test; Tau^2 = Kendall's Tau test; df = degree of freedom; p-value.



Mean = mean of the groups; SD = standard deviation; Weight = statistical relevance of the study; IV = inverse variance; CI = confidence interval; Fixed = fixed effect; I^2 = heterogeneity index; Z = global effect test; Chi^2 = Chi-square test; Tau^2 = Kendall's Tau test; df = degree of freedom; p-value.

Figure 2. Meta-analysis results regarding the effect of Pilates on pain during pregnancy and labor.

muscles. Pilates exercise contributes to strengthening the pelvic floor and preventing and treating dysfunctions caused by pregnancy[7]. The current guidelines recommend moderate-intensity exercise during pregnancy[17,18].

According to the results of this meta-analysis, it was seen that Pilates exercise was not effective in reducing pain during pregnancy. Similar to the results of this study, Mazzarino et al. reported that there was insufficient evidence that Pilates relieved low back pain during pregnancy[19]. However, in the meta-analysis study by Mendo and Jorge, it was expressed that Pilates was useful against pain during pregnancy[7]. The study by Sonmezer et al. stated that Pilates had a positive effect on reducing pain during pregnancy[2]. The study by Canarslan and Albayrak revealed that Pilates reduced pain during pregnancy[20]. In another study, Pilates was demonstrated to be an effective, healthy, and applicable method to reduce pain during pregnancy[1]. Although there are studies stating that Pilates provides benefits regarding its effect on pain during pregnancy[1,2,7,20], more randomized controlled trials are needed on this subject.

It is reported that Pilates exercise during pregnancy is beneficial in terms of preparing low-risk pregnant women for labor[14]. As a result of enhancing the flexibility of the trunk and pelvic floor muscles and improving proper breathing, Pilates exercise can facilitate the labor process and reduce pain during labor[3,21].

In the current meta-analysis study, Pilates exercise during pregnancy was found to be effective in reducing pain intensity during labor. In the study, Rodríguez-Díaz et al. showed that 8-week Pilates exercise during pregnancy reduced pain during labor and the use of analgesics, which resulted in significant improvements in labor[21]. A study emphasized that regular Pilates exercise during pregnancy strengthened the pelvic floor muscles, reduced pain, and decreased the need for epidural anesthesia during labor[3]. Another study elucidated that the Pilates group felt less pain during labor compared to other groups[11].

Limitations

The strengths of this study are that there is no high level of bias in the studies included in the systematic review and meta-analysis, the results are based on reliable analysis methods, the subject is evaluated from different perspectives, and the results obtained are supported by the results reported in previous studies. A limitation of this study is that the search was done only in Turkish and English languages.

CONCLUSION

As a result of this systematic review and meta-analysis, it was found that Pilates exercise during pregnancy was not effective in reducing the pain during pregnancy, but it was effective in reducing labor pain. These results are valuable since they include the results of randomized controlled trials on the subject.

Pilates, which is a low- and moderate-intensity exercise, is a low-cost, easily applicable, non-pharmacological method with no side effects. Therefore, it is important to increase the use of Pilates exercise during pregnancy and inform and educate healthcare professionals on this subject. To identify the effect of Pilates exercise on pain during pregnancy and labor, it is recommended to conduct randomized controlled quantitative and qualitative studies that reveal the experiences of pregnant women.

AUTHORS' CONTRIBUTIONS

TY: Conceptualization, Date curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing– review & editing. **ÖT:** Conceptualization, Date curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **SG:** Conceptualization, Date curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **HDK:** Conceptualization, Date curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Importance of targeted next-generation sequencing in pediatric patients with developmental epileptic encephalopathy

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SUMMARY

OBJECTIVE: Childhood epilepsy is a common neurological disorder with a prevalence of 300–600 cases per 100,000 people. It is associated with refractory epilepsies, global developmental delay, and epileptic encephalopathies, causing epileptic syndromes characterized by cognitive and behavioral disorders.

METHODS: In this retrospective cohort study, patients with refractory epilepsy and global developmental delay, defined as epileptic encephalopathy, who applied to the Aydın 7Maternity and Children's Hospital Genetic Diagnosis Center and were followed in the pediatric neurology clinic of our hospital, between July 2018 and July 2021, were included.

RESULTS: Targeted next-generation sequencing molecular genetics results were reviewed, and *3 ALDH7A1, 1 AARS, 3 CACNA1A, 1 CTNNB1, 1 DCX, 2 DBH, 2 DOCK7, 1 FOLR1, 2 GABRB3, 2 GCH1, 1 VGRIN2B, 1 GUF1, 3 KCNQ2, 2 KCNT1, 1 NECAP1, 1 PCDH19, 1 PNPO, 1 SCN8A, 1 SCN9A, 4 SCN1A, 2 SLC25A22, 1 SLC2A1, 2 SPTAN1, 2 SZT2, 4 TBC1D24, 2 TH, and 1 PCDH19* (X chromosome) mutations were detected in three of the patients using the next-generation sequencing method.

CONCLUSION: Although the development of gene panels aids in diagnosis, there are still unidentified disorders in this illness category, which is highly variable in genotype and phenotype. Understanding the genetic etiology is vital for genetic counseling and, maybe, the future development of remedies for the etiology.

KEYWORDS: Epilepsy. Neurological disorder. Pediatrics. Next-generation sequencing.

INTRODUCTION

Childhood epilepsy is a common neurological disorder with a prevalence of 300–600 cases per 100,000 people. Refractory epilepsy is characterized by the persistence of seizures despite treatment with two or more antiepileptic drugs, either separately or together, for an appropriate period of time and dose. It affects approximately 30% of children diagnosed with epilepsy[1,2].

It is associated with refractory epilepsies, global developmental delay (GDD), and epileptic encephalopathies (EE), causing epileptic syndromes characterized by cognitive and behavioral disorders. These diseases exhibit diversity in terms of etiology, age of onset, seizure types, electroencephalography (EEG) findings, and prognosis. Childhood epilepsy is a clinically heterogeneous neurological disorder. There is frequently a genetic etiology at play, which is defined as the reason for the cognitive dysfunction brought on by EE, refractory epilepsy, and ongoing epileptiform activity[3,4].

Knowing the etiology can help with treatment and prognosis for epilepsy patients. Due to the complexity of the genetic structure of epilepsy, there are many options for diagnostic research. The developments that have emerged in recent years to reveal the genomic etiology, particularly next-generation sequencing (NGS), have provided the opportunity to get rapid results. Patients can be genetically diagnosed in whole-exome studies using NGS platforms[5]. Recently, the importance of targeted next-generation sequencing panels (T-NGS) for epilepsy in revealing the genetic etiology has been increasing[2,4]. In studies, up to 265 monogenic epilepsy-associated genes have been investigated for being associated with a wide variety of epilepsy syndromes[6].

In this study, our aim was to determine the clinical features of patients followed up in our clinic whose genetic etiology was determined using the T-NGS method.

METHODS

In this retrospective cohort study, patients with refractory epilepsy and GDD, defined as epileptic encephalopathy, who

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applied to the Maternity and Children's Hospital Genetic Diagnosis Center and were followed in the pediatric neurology clinic of our hospital between July 2018 and July 2021, were included. The reason for the admission of the patients was to identify the underlying genetic causes. The patients' age, gender, clinical features, electroencephalography examinations (EEG), neuroimaging findings, biochemical and metabolic tests, and T-NGS molecular genetic research results for epileptic encephalopathy were reviewed by screening electronic patient files. All epilepsy diagnoses, seizure types, and epilepsy syndromes were determined and classified according to the ILAE (International League Against Epilepsy) 2017 Exclusion criteria, which included seizures caused by non-genetic factors such as an acquired or structural brain injury (including traumatic brain injury, encephalitis, vasculitis, hypoxia, abscess, neoplasm, metabolic disturbance, and toxicity). Brain magnetic resonance imaging (MRI) was performed in all patients, and the genes identified through T-NGS are presented in Table 1.

Genomic DNA was extracted from the peripheral blood, and NGS was performed by capturing the coding regions and splice sites of targeted genes using a commercial NGS kit (Celemics, South Korea). The list of targeted genes in the panels is provided in Table 1. NGS was performed on an Illumina MiSeq platform (Illumina, San Diego, CA, USA). The sequencing reads were aligned to the human genome reference (GRCh37: Genome Reference Consortium human build 37) using Burrows-Wheeler Alignment Tool (BWA). Subsequently, BAM files were sorted, indexed, and de-duplicated using SAMtools and Picard tools. For the filtering process, exonic and splicing variants, including mis-/nonsense variants, and indels were selected. Rare variants with minor allele frequency less than 0.001 were filtered. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines[6]. All variants identified by NGS were confirmed through Sanger sequencing. Patients and parents were tested to determine whether the pathogenic variations were *de novo* or inherited.

A custom target enrichment panel was designed to capture 54 genes related to epileptic encephalopathies (Table 1). All exons, the 25 base pairs of the intronic flanking region, and 5′ and 3′ untranslated region of each gene were sequenced. After library enrichment and quality control, the samples were sequenced using the MiSeq platform (Illumina, San Diego, CA, United States). Raw reads were trimmed with Trimmomatic and mapped to the reference human genome (hg19) using BWA. Duplicates were removed using SAMTools, and realignment across indels and base quality recalibration were performed using GATK. Annotation of detected variants was performed using Illumina BaseSpace Variant Interpreter, InterVar, Franklin, VarSome, ClinVar, OMIM, and Pubmed. Variants with a frequency higher than 0.5% were filtered out. dbNSFP (containing SIFT, PolyPhen-2, LRT, and Mutation Taster) was used to predict the pathogenicity and deleteriousness of variants. Rare variants were classified according to the ACMG/AMP variant interpretation framework[7].

RESULTS

A total of 198 patients were included in this retrospective cohort study. The mean age of the patients was 7.4±5.8 standard deviation (SD) (age range of 8 months to 16 years). An identifiable underlying genetic cause was identified in 48 (25%) out of 198 patients. The F/M ratio of patients with genetic mutations was found to be 6:10. The *3 ALDH7A1, 1 AARS, 3 CACNA1A, 1 CTNNB1, 1 DCX, 2 DBH, 2 DOCK7, 1 FOLR1, 2 GABRB3, 2 GCH1, 1 VGRIN2B, 1 GUF1, 3 KCNQ2, 2 KCNT1, 1 NECAP1, 1 PCDH19, 1 PNPO, 1 SCN8A, 1 SCN9A, 4 SCN1A, 2 SLC25A22, 1 SLC2A1, 2 SPTAN1, 2 SZT2, 4 TBC1D24, 2 TH*, and *1 PCDH19* (chromosome X) mutations were detected in three patients. All mutation distributions are shown in Table 2. The age of seizure onset in our patients was 14.8 months. Four

Table 1. Genes identified for targeted next-generation sequencing that are thought to be related to magnetic resonance imaging disorders in the literature.

EEF1A2	PNPO	DOCK7	ARHGEF9	AARS1	GNAO1
ST3GAL3	SLC1A2	GUF1	TBC1D24	HCN1	SCN1A
ARV1	GABRB3	SLC25A1	PNKP	PIGA	PLCB1
DCX	MAOA	NECAP1	SCN8A	KCNQ2	CACNA1A
KCNB1	KCNT1	SPTAN1	DNM1	PCDH19	STXBP1
SCN2A	ARX	CDKL5	ITPA	TH	KCNQ3
DBH	FOLR1	ALG13	ALDH7A1	SCN9A	SLC25A12
SLC2A1	GABRA1	SLC13A5	SLC35A2	SLC12A5	KCNA2
GCH1	FRRS1L	SZT2	WWOX	GRIN2B	GLRA1

patients were diagnosed with mental retardation (2 with moderate mental retardation and 2 with severe mental retardation). Notably, 12 patients were being followed up by the child psychiatry clinic due to autism spectrum disorder. A total of 198 patients were included in this retrospective cohort study. The mean age of the patients was 7.4±5.8 standard deviation (SD) (age range of 8 months to 16 years) (Table 2).

Metabolic examination tests were performed in all patients, and no specific findings indicative of a disease were detected. Cranial imaging was performed in all patients. There was no structural anomaly that could cause a seizure. In contrast, hippocampal sclerosis was detected in a patient with Dravet syndrome, which is secondary to frequently recurring long-term febrile seizures. Notably, 6 patients were diagnosed with West syndrome, 2 patients developed Lennox-Gastaut syndrome, and 12 patients had a history of febrile convulsions. Ataxia was observed during the neurological evaluation of the patient with the *CACNA1A* mutation.

Table 2. Distribution and location of mutations detected in patients.

Number of patients	Gene	Mutation location	ACMG pathogenicity
3	*ALDH7A1*	c.1597delG (p.Ala533ProfsTer18) c.1597delG (p.Ala533Profs*18) c.328C>T .p.Arg110Ter	Pathogenic (PP5, PVS1, PM2)
1	*AARS*	c.601G>A (p.Ala201Thr)	VUS (PM2)
3	*CACNA1A*	c.4687G>A (p.Val1563Met), c.6409G>C (p.Asp2137His)	Likely pathogenic (PM2, PP3, PP2), VUS (PM2, PP2)
2	*CTNNB1*	c.1320A>C p.(Gln440His)	VUS (PM2, PP2)
1	*DCX*	c.1120A>T (p.Thr374Ser)	VUS (PM2, PP2)
2	*DBH*	c.1627C>A (p.Pro543Thr), c.1025-6T>A	VUS (PM2), VUS (PM2, BP4)
2	*DOCK7*	c.4073G>A p.(Arg1358Gln), c.1724A>G p.(Asn575Ser)	VUS (PM2, PP2), VUS (PM2, PP2, BP4)
1	*FOLR1*	c.493+2T>C	VUS (PVS1, PP5, BS2)
2	*GABRB3*	c.4073G>A p.(Arg1358Gln), c.56G>A (p.Gly19Glu)	VUS (PM2, PP2, PP3)
2	*GCH1*	c.333G>A (p.Glu111=)	VUS (PM2, BP7)
1	*GRIN2B*	c.2642A>G (p.Gln881Arg)	VUS (PM2, PP2, BP4)
2	*GUF1*	c.1402_1403delGA (p.Glu468Ilefs*15)	Likely pathogenic (PVS1, PM2)
3	*KCNQ2*	c.1741C>T (p.Arg581*), c.88G>A (p.Gly30Ser), c.2173C>T (p.Arg725Cys)	Pathogenic (PVS1, PM2, PP5), VUS (PM2, PP2)
2	*KCNT1*	c.2594+7C>T, c.1210G>A (p.Val404Met)	VUS (PP3, BP6), VUS (PM2)
1	*NECAP1*	c.812A>G (pAsn271Ser)	VUS (PM2, BP4)
1	*PCDH19*	c.2838G>A (p.Pro543Thr)	VUS (PP2, PM2, BP4)
1	*PNPO*	c.20G>A (p.LysY7Asp)	VUS (PM2, PP2, BP4)
2	*SCN9A*	c.1828C>A p.(Pro610Thr), c.3267C>A (p.Asn1089Lys)	VUS (PM2, BP4, BP7),VUS (PM2, BP7)
4	*SCN1A*	c.812A>G (pAsn271Ser), c.1625G>A (p.Arg542Gln), c.4324T>A (p.Tyr1442Asn), c.3840_3843delTGTT (p.Ile1280Metfs*8), c.80G>C (p.Arg27Thr)	Pathogenic (PM2, PVS1), VUS (PP2, BP4)
2	*SLC25A12*	c.784G>A (p.Glu262Lys), c.279G>C (p.Gln93His)	Likely pathogenic (PM2, PP3) VUS (PM2, PP2)
1	*SLC25A1*	c.376C>T (p.Arg126Cys)	VUS (PM2, BP7)
2	*SPTAN1*	c.2119G>A (p.Gly707Ser), c.1143A>C (p.Lys381Asn)	Likely pathogenic (PM2, PP3, PP2), VUS (PM2, PP2, BP4)
2	*SZT2*	c.9458G>A (p.Arg3153His), c.7342C>T (p.Arg2448Cys)	Likely Benign (PM2, BP4), VUS (PM2)
4	*TBC1D24*	c.418C>G (p.Leu140Val), c.1015A>G (p.Asn339Asp), c.1020C>G (p.Phe340Leu), c.871G>A (p.Ala291Thr)	VUS (PM2), VUS (PM2), VUS (PM2), VUS (PM2)
2	*TH*	c.1144A>G (p.Ile382Val), c.440G>A (p.Arg147Gln)	VUS (PM2, PP2), VUS (PM2, PP2)
1	*PCDH19*	c.1238G>T (p.Arg413Leu)	VUS (PP2, PM2, BP4)

DISCUSSION

Epileptic encephalopathies with severe electroencephalography findings that may result in severe neurological deficits and drug-resistant seizures that occur in the first years of life have several differences according to etiology, phenotype, and prognosis. While the etiology is mostly dependent on symptomatic causes (e.g., Ohtahara syndrome and West syndrome), in some syndromes (e.g., Dravet syndrome), genetic etiology plays a significant role[1,2,4]. In this study, out of 16 patients, 4 were followed up for West syndrome, 2 for Lennox-Gastaut syndrome, and 1 for Dravet syndrome, while a definitive diagnosis could not be made in 9 patients due to the absence of findings that would indicate a specific syndrome. An identifiable underlying genetic cause was identified in 48 (25%) out of 198 patients. In a study conducted by Ara K. et al., the rate was found to be 37.1%, which is higher than this study. However, in previous studies, this rate ranged between 20% and +2% and these results are in agreement with this study[8-11]. While the mutation found in 10 (5.5%) patients was considered definitively pathogenic, the changes found in 11 (5.5%) patients were determined as likely pathogenic. In the studies conducted by Ara k Parrini E and Trump N, this rate was found to be between 19.5 and 26.6%[9-11]. The high number of patients observed in these studies is thought to be effective in obtaining these results. Among them, 23 (11.1%) patients with other mutations were evaluated as VUS. This probably explained the etiology of cases with VUS. In this study, the diagnostic rate for epilepsy was 25% using whole-exome sequencing. With NGS systems, faster epilepsy genes will be detected. In other studies, these rates varied between 14.5 and 41.6%[8-10].

West syndrome developed in four patients (25%), and LGS developed after West syndrome in two patients. In the literature, the rate of LGS developing after infantile spasms is reported to be 20–40%. In the study, in which 98 patients with West syndrome were followed up for 3 years, LGS developed in 48% of patients. In this study, in which no relationship was found between the development of LGS and the age of onset of West syndrome or the etiology of West syndrome, the risk of developing LGS was lower in patients who received a ketogenic diet, prednisone, or ACTH[12,13]. Six of our patients had a history of febrile convulsions before the onset of seizures. The mean age at which febrile seizures were seen was 1.4 years (with an age range of 1–3 years). In a study conducted on 38 LGS patients, febrile seizures were observed in 3 patients (7.9% of patients with LGS) before seizures started, and the mean age at which febrile seizures were observed was reported to be 6 months[14]. The rate of febrile seizures (12/16) among the patients included in this study was higher than that of the healthy population.

The term "epileptic encephalopathy" has been used since the late 1970s to refer to certain devastating epilepsies seen early in life. Epileptic encephalopathies include epileptic syndromes characterized by cognitive and behavioral disorders. These diseases exhibit diversity in terms of etiology, age of onset, seizure types, electroencephalography (EEG) findings, and prognosis. Epileptic encephalopathies are severe syndromes characterized by drug-resistant, generalized or focal seizures, cognitive dysfunction, decline, and severe electroencephalographic findings that occur early in life. The International League Against Epilepsy (ILAE) defines epileptic encephalopathies as conditions where "epileptiform abnormalities are considered to cause progressive impairment of cerebral function." Ictal and interictal epileptic discharges are age-related and constitute the main cause of cognitive decline. In some cases, clinical and EEG abnormalities continue as the child grows, and transformation from one type to another may be observed[15,16]. All the patients in this study were diagnosed with epilepsy after seizures, and with the progression of the disease, the diagnosis of epileptic encephalopathy was done at the center.

Two of our patients had moderate and two had severe intellectual disabilities. All other patients were followed up with a diagnosis of autism spectrum disorder. Jansen et al. reported these rates as 45.45% (5 out of 11 patients) and 54.55% (6 out of 11 patients) in their series[17]. Akiyama et al. reported that 22.58% of the patients did not have word output (7 out of 31 patients) in their study[18]. While a patient with moderate intellectual disability was partially dependent on the help of their relatives, a patient with severe intellectual disability was completely dependent on the help of their relatives in their daily life activities. In other studies, these rates were 33.3% (8 out of 24) and 54.2% (13 out of 24), 14.28% (2 out of 14), and 71.42% (10 out of 14)[17,18]. Cranial imaging could be performed in all patients with autism and epilepsy comorbidity. These patients' MRIs revealed no structural abnormalities.

The MRI of our patient with Dravet syndrome showed hippocampal sclerosis. Additionally, the patient had findings of autism spectrum disorder. One study reported that 22.4% (8 out of 58 patients) with Dravet syndrome had abnormal cranial MRI findings, 13.79% (8 out of 58 patients) had cortical atrophy, 1.72% (1 out of 58) had cerebellar atrophy, and 1.72% had hippocampal sclerosis[18,19]. Similar to other reported cases, our patient had a history of frequent febrile seizures, cognitive decline, and status epilepticus after phenytoin. Treatment options with proven efficacy in the treatment of Dravet syndrome include stiripentol, valproic acid, clobazam and other benzodiazepines, topiramate, levetiracetam, and a ketogenic diet. Increased body temperature,

lamotrigine, phenytoin, vigabatrin, oxcarbazepine, and carbamazepine may exacerbate seizures[20,21].

The limitations of this study are as follows. The number of patients was small in some syndromes, the collection of clinical data of patients from their childhood was found to be difficult, some patients missed follow-up examinations for a long time, and some patients could not be reached. The small number of participating centers and thus the patient number included in the genetic analyses are other limitations.

CONCLUSION

Epileptic encephalopathies are severe and refractory epilepsies requiring regular follow-up, clinical evaluations, and increased social support. Genetic diagnoses have been made in some cases, but uncertainty persists for most, posing a serious health problem. Gene panels aid diagnosis, but undiagnosed conditions remain in this genetically diverse disease group. Understanding the genetic etiology is crucial for counseling and future treatment development.

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AUTHORS' CONTRIBUTIONS

SB: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **SK:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **ÖB:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft.

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ORIGINAL ARTICLE

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Profile of oropharyngeal dysphagia patients in a teaching hospital in Northern Brazil: a descriptive cross-sectional study

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SUMMARY

OBJECTIVE: The aim of this study was to describe the profile of patients with oropharyngeal dysphagia in a teaching hospital in the public health system in northern Brazil.

METHODS: This is a descriptive cross-sectional study. All procedures of this study were approved by the ethics committee. A convenience sample composed of participants aged >18 years, of both sexes, with any underlying pathology admitted to the medical clinic on exclusive oral feeding, alternatively enteral or gastric tube feeding (Gastrostomy), or associated by both routes, whose swallowing assessment was performed by a Speech-Language Pathologist. Data from the database/medical records were investigated from March 2020 to September 2021.

RESULTS: The sample consisted of 44 patients diagnosed with oropharyngeal dysphagia, with a higher frequency of males (63.64%) aged over 60 years (70.45%). Almost half of the evaluated patients were diagnosed with neurological disorders (47.73%) and had dysphagia associated with other underlying diseases (31.82%). Excluding patients with neurological disorders, trauma/polytrauma, and respiratory disorders from the last group, some patients (11.36%) had two concomitant underlying diseases.

CONCLUSION: According to the sample of this study, the profile of oropharyngeal dysphagia patients includes pneumonia, respiratory failure, bronchoaspiration, and the consequent need for ventilatory support.

KEYWORDS: Swallowing disorders. Deglutition disorders. Public health. Epidemiology.

INTRODUCTION

Swallowing is the result of fine neuromotor control responsible for transporting the food bolus from the mouth to the stomach in a safe and effective way. Some patients admitted to hospital units have difficulty in transporting food from the mouth to the stomach (dysphagia)[1]. This difficulty is accompanied by coughing, choking, pain when swallowing, and pharyngeal globus[2]. Dysphagia is a commonly observed symptom in neurological and respiratory disorders. According to Bassi et al.[3], hospitalized patients with respiratory diseases had a higher risk index for oropharyngeal dysphagia. Another study showed the presence of oropharyngeal dysphagia in 80% of hospitalized patients[4].

In addition to dysphagia related to neurological disorders, there are other causes that occur due to different conditions, known as mechanical dysphagia, in which the anatomical structures responsible for swallowing suffer some structural damage, as occurs in head and neck cancers, cardiovascular diseases, lung diseases, and respiratory diseases[5]. When difficulty in swallowing is associated with respiratory diseases, there is a possibility of bronchoaspiration[6], in which entry of food or fluids into the lower airways can generate pneumonia and death[7]. It is also known that the elderly are more susceptible to dysphagia due to the diseases, such as stroke and cardiovascular diseases, which accompany this condition[4,5].

However, considering the period of the COVID-19[6] pandemic in Brazil, there are still no studies that show the health profile of these patients after the pandemic. Therefore, it is still necessary to understand the presentation of dysphagia and its impact on the general condition of the patient after the COVID-19 pandemic in order to propose measures to minimize or interrupt the resulting sequelae. An opportunity for investigations in this scenario is scientific research in Teaching Hospitals, as these are related to care in the unified health system and receive patients from different regions of Brazil. Thus, the objective of this study was to describe the profile of patients with oropharyngeal dysphagia in a teaching hospital in the public health system in northern Brazil.

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METHODS

Study design

A descriptive cross-sectional study was carried out according to STROBE guidelines. We included all underlying diseases, which were divided into large groups: neurological disorders, trauma/polytrauma, respiratory disorders, COVID-19 (isolated from respiratory diseases due to its peculiarities), others (which include cancers, cardiovascular diseases, and gastrointestinal diseases), two underlying diseases, and three or more underlying diseases.

Sociodemographic data and variables such as feeding path, underlying disease, and diagnosis of dysphagia were obtained through analysis of the patients' medical records. The exposure variables were sociodemographic characteristics and the outcome variable was hospital discharge with exclusive oral feeding.

Context

A study was carried out at the medical clinic of a referral hospital in the city of *Blinded for review*. Data from medical records were investigated from March 1, 2020 to September 1, 2021. This is a public hospital, classified as a size III hospital (medium and high complexity), accredited as a specialized health care service. The results of the patients' characteristics were described by relative and absolute frequencies using the Stata program (Statistics/Data Analysis). We used the chi-square test to determine the association between underlying disease and diagnosis of dysphagia.

Participants

All procedures of this study were approved by the ethics committee (*Blinded for review* 5.081.409) according to ethical guidelines recommended in Brazil. A convenience sample composed of participants aged >18 years, of both sexes, with any underlying pathology admitted to the medical clinic on exclusive oral feeding, alternatively enteral or gastric tube feeding (Gastrostomy), or associated by both routes, whose swallowing assessment was performed by a Speech-Language Pathologist. Patients on zero or exclusive parenteral diets, as well as medical records with incomplete information on the study variables were excluded.

Variables

Data on demographic and health characteristics of patients (age, sex, marital status, underlying disease, and comorbidities were collected and documented in a collection protocol prepared by the researchers. We evaluated patients with dysphagia, according to a speech-language diagnosis, in order to determine the repercussion of dysphagia in patients with any underlying pathology. Based on this, we sought to identify the main complications associated with dysphagia that could further compromise the health status of these patients.

Sociodemographic data and variables such as feeding path, underlying disease, and diagnosis of dysphagia were obtained through analysis of the patients' medical records. The information collected was documented in a collection protocol prepared by the researchers.

Measurements

Data collection instrument covers the following variables: qualitative or dynamic policy to determine the patient's month, anatomy, and age; qualitative nominal dichotomies for gender, marital status, underlying disease, and dysphagia diagnosis; qualitative nominal polychotomous to detect via feeding, symptoms of dysphagia, degree of dysphagia, and complications during hospitalization; and nominal mechanical decisions for hospital treatment, airway, days of treatment in an invasive care unit, and intensive food treatment.

Bias

An expert in dysphagia linked to the Federal Council of Speech-Language Pathologists was responsible for data collection. We created an electronic data collection form using the Excel software to build the database.

Statistical analysis

In the statistical analysis, the results of the patients' characteristics were described by relative and absolute frequencies using the Stata program (Statistics/Data Analysis). Missing data were disregarded and, therefore, excluded from this research.

RESULTS

We recruited 108 patients and excluded 64 (59.26%) patients due to the absence of diagnosis of dysphagia. Thus, the final sample is composed of 44 participants. Table 1 shows a higher frequency of oropharyngeal dysphagia in males (63.64%), a lower frequency in young adults, and a higher incidence of dysphagia in adults aged ≥60 years (70.45%).

Regarding dysphagia-associated diseases, most patients (47.73%) have neurological disorders, followed by 31.82% with dysphagia associated with other underlying diseases, 2.27% with trauma/polytrauma, 2.27% with respiratory diseases, and 2.27% with COVID-19. Besides, 11.36% of patients had two underlying diseases, and 2.27% had ≥3 underlying diseases (Table 1). Mean complications during hospitalization are related to respiratory diseases such as pneumonia, bronchoaspiration, respiratory failure, and the need for ventilatory support (Table 2).

Table 1. Sample characteristics (n=44).

Variables	n (%)	Cum.
Sex		
Male	28 (63.64)	63.64
Female	16 (36.36)	100.00
Age (years)		
18–24	1 (2.27)	2.27
24–49	5 (11.36)	13.64
49–60	7 (15.91)	29.55
>60	31 (70.45)	100
Underlying diseases		
Neurological disorders	21 (47.73)	47.73
Trauma/polytrauma	1 (2.27)	50.00
Respiratory diseases	1 (2.27)	52.27
COVID-19	1 (2.27)	54.55
Other	14 (31.82)	86.36
2 underlying diseases	5 (11.36)	97.73
≥3 underlying diseases	1 (2.27)	100.00

Table 2. Complications under hospitalization (n=44).

Variables	n (%)	Cum.
Pneumonia	1 (2.27)	84.09
Pneumonia and bronchoaspiration	1 (2.27)	86.36
Respiratory failure	3 (2.27)	93.18
Respiratory failure	3 (2.27)	100.00

DISCUSSION

Mean outcomes

In this study, there was a higher frequency of males in the diagnosis of dysphagia associated with underlying diseases. The number of patients are similar among the studies carried out (62.5% of involvement in males)[8-10]. Regarding age, in this study, there was a higher frequency of elderly people, corroborating the dysphagia literature, with 16–22% of elderly people over 50 years old and 90% of patients with a mean age of 83 years[8,11]. The age of participants in a study on a higher frequency of dysphagia in ischemic stroke ranged from 30 to 96 years, with a mean of 68.62 years[10].

Regarding the underlying diseases, there was a higher frequency of neurological disorders (corroborating with the literature). In the study by Gaspar et al., out of 35 patients diagnosed with stroke, 21 had neurogenic dysphagia[9]. Ferreira et al. also observed a predominance of neuropathies (53.4%) and severe neurogenic oropharyngeal dysphagia (37.2%)[12]. Almeida et al.[13] emphasized that a higher frequency of oropharyngeal dysphagia is high in individuals diagnosed with stroke after cardiac surgery: of the 25 (100%) individuals, 24 (96%) had some degree of oropharyngeal dysphagia in the clinical evaluation. It was found that 41.66% had severe dysphagia, 33.66% had moderate dysphagia, and 25% had mild dysphagia.

Regarding dysphagia in patients with orthopedic trauma injuries or multiple traumas as underlying diseases, in this study, there was a low frequency, which is not consistent with the literature dealing with this topic. In a hospital specializing in traumatic injury, a study was carried out on 229 patients, of whom 64 (27.9%) had complaints in swallowing solid foods and 26 (11.4%) had complaints for liquids[14]. The low frequency of dysphagia in multiple traumas is justified by the fact that the hospital in this research has exclusive wards for trauma and multiple traumas, an orthopedics and neurology sector, and this research was carried out on patients admitted exclusively to the institution's medical clinic.

Regarding respiratory diseases, although the frequency was low, when the variable complications during hospitalization were evaluated, 18.18% (n=08) of patients presented pneumonia, bronchoaspiration, respiratory failure, and the need for ventilatory support as the main complications. These complications may result from oropharyngeal dysphagia, depending on the degree of dysphagia. Bassi et al. determined the risk group for dysphagia in a hospital in which patients admitted with respiratory diseases had a higher risk index for oropharyngeal dysphagia[3]. Gazzana et al. found that the presence of dysphagia is most common in patients with chronic respiratory diseases[15].

The low frequency of COVID-19 as an underlying disease in this study is justified by the fact that the hospital has a specific ward for the treatment of patients affected by this injury. Cardoso[16] highlighted a close relationship between COVID-19 and dysphagia, as shown by the fact that the frequency of swallowing disorders was higher when associated with the factors like age and use of tracheostomy in individuals who were infected by COVID-19[6].

Regarding groups termed other diseases, these were the symptoms mainly distributed among heart diseases, degenerative diseases, gastrointestinal diseases, kidney diseases, and cancers. According to the literature, the comorbidities most commonly associated with patients with symptoms and signs of dysphagia were chronic obstructive pulmonary disease, systemic arterial hypertension, congestive heart failure, diabetes mellitus, and myocardial infarction[3].

We highlighted the need to perform dysphagia screening using validated protocols in order to determine the safest feeding route for the patient. Of the 44 patients analyzed, regardless of

underlying diseases, dysphagia was present to varying degrees, which may have been the cause of some, if not all, respiratory problems observed in 18.18% of patients.

Dysphagia has been the subject of studies over the past decades, especially as a result of its multivariate sequelae, which often go unnoticed as the main aggravating factor of the patient's clinical situation. This may be due to the fact that dysphagia is rarely addressed and studied in health professionals' training centers. Studies are clear in pointing out the destructive and often deadly comorbidities of dysphagia, as is the case with bronchoaspirations.

The lack of a unified and validated protocol in the institution where the research was carried out emphasizes the need for new similar assessments, this time after the introduction of validated protocols for more accurate assessments. However, it should be noted that, although there is no validated evaluation protocol, the institution's speech therapists have a wide range of experience in the area and have performed an excellent job, based on a comprehensive and correct clinical evaluation, from the point of view of the technician. We also emphasized the importance of continuing education in the process of consolidating transdisciplinary monitoring in dysphagia. Without it, the advantages such as the introduction of dysphagia specialists in the hospital team would be unlikely.

This study needs to be addressed. For example, the hospital surveyed in this study does not have validated protocols in the dysphagia estimation flowchart, and there are some missing data that reduced the sample size. In addition, since this is a descriptive study with convenience sampling, further research is suggested.

CONCLUSION

According to the sample of this study, the profile of oropharyngeal dysphagia patients includes pneumonia, respiratory failure, bronchoaspiration, and the consequent need for ventilatory support.

AVAILABILITY OF DATA AND MATERIALS

The data and materials in this paper are available from the corresponding author on request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Research Ethics Committee (protocol number 5.081.409). All respondents participated in this study freely and with consent.

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AUTHORS' CONTRIBUTIONS

IMPG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **APS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **MMZ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **AMB:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **FRPQ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Evaluation of the relationship between blood cell markers and inflammation, disease activity, and general health status in ankylosing spondylitis

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SUMMARY

OBJECTIVE: The aim of this study was to assess the relation of systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index with disease activity, functional status, and general health status in ankylosing spondylitis.

METHODS: Patients with ankylosing spondylitis and healthy volunteers were included in this cross-sectional study. Demographic data; disease activity measurements such as the Bath Ankylosing Spondylitis Disease Activity Index, the Ankylosing Spondylitis Disease Activity Score with C-reactive protein, and the Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate; functional status such as the Bath Ankylosing Spondylitis Functional Index; and general health status such as the Assessment of Spondyloarthritis International Society Health Index of the patients were recorded. C-reactive protein, erythrocyte sedimentation rate, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index values were recorded. Patients were grouped as active and remission according to the Bath Ankylosing Spondylitis Disease Activity Index score and as inactive-low and high-very high disease activity according to the Ankylosing Spondylitis Disease Activity Score. The correlation of laboratory parameters with disease-related parameters was tested.

RESULTS: The indexes were significantly higher in patients compared to controls ($p<0.001$, for platelet to lymphocyte ratio $p=0.03$). No significant differences existed in any blood cell-derived indexes among patient groups categorized by disease activity ($p<0.05$ for all). Systemic immune inflammation index was weakly correlated with Ankylosing Spondylitis Disease Activity Score with C-reactive protein ($\rho=0.197$ and $p=0.049$) and Ankylosing Spondylitis Disease Activity Score-erythrocyte sedimentation rate ($\rho=0.201$ and $p=0.045$). Systemic immune inflammation index was not correlated with Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, and Assessment of Spondyloarthritis International Society Health Index. No correlation was found between other indexes and disease-related variables. Platelet to lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index showed a weak positive correlation with C-reactive protein and erythrocyte sedimentation rate ($\rho=0.200–0.381$).

CONCLUSION: Systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index can be used to indicate systemic inflammatory burden in ankylosing spondylitis patients. However, these indexes are not effective in indicating patients' disease activity, general health status, and functional status.

KEYWORDS: Ankylosing spondylitis. Mediators of inflammation. Blood cell count. Lymphocytes.

INTRODUCTION

Ankylosing spondylitis (AS), the prototype of spondyloarthritis, is a rheumatic condition with an unknown etiology that causes chronic inflammation of axial structures, including sacroiliac joint, spine, and paraspinal soft tissues. Low back pain and stiffness are frequent complaints, and extra-articular signs/symptoms can be observed throughout the disease's progression. These include anterior uveitis, inflammatory bowel disease, coronary heart disease, and osteoporosis, all of which are closely related to inflammation[1,2]. Therefore, the use of reliable markers to evaluate inflammation is crucial for disease monitoring and determining clinical outcomes.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), two non-specific inflammatory biomarkers, are frequently used to assess the inflammatory process. Nevertheless, serum levels of these markers are influenced by a variety of disorders, and normal levels do not reliably prevent active disease, especially in different rheumatic conditions[3]. Complete blood cell count parameters, including neutrophil, monocyte, lymphocyte, and platelet counts, and

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their derived indexes such as the neutrophil to lymphocyte ratio (NLR), the monocyte to lymphocyte ratio (MLR), and the platelet to lymphocyte ratio (PLR), the systemic immune inflammation index (SII), the systemic inflammation response index (SIRI), and the systemic inflammation aggregate index (AISI) are cost-effective and not time-consuming tests that have served as indicators of inflammation in a variety of rheumatic diseases and other inflammatory medical conditions[4-6]. Systemic inflammation is closely connected with variations in these inflammatory indexes.

Recently, several studies and meta-analyses have provided evidence that NLR, LMR, and PLR are strong indicators of inflammation in AS[7,8]. However, research on the association between these measures and disease activity has provided contradictory results in patients with spondyloarthritis[9,10]. On the contrary, studies on SII, SIRI, and AISI focus on rheumatoid arthritis and other inflammatory conditions[6,11,12]. The data on this issue in patients with AS are still quite limited[6,13].

To the best of our knowledge, the potential of SIRI and AISI in determining chronic inflammatory burden in AS has not been previously documented. For this reason, the aim of this study was to investigate the role of cost-effective and easily calculated indexes in exhibiting systemic inflammation, disease activity, and general health status in AS.

METHODS

Participants and study concept

This study was executed between September 2022 and January 2023 at a university hospital. In this cross-sectional study, patients were enrolled in an outpatient clinic by rheumatologists and physiatrists during routine evaluations. The inclusion criteria were (i) diagnosed as AS according to Modified New York criteria[14] and (ii) ≥18 years of age. The exclusion criteria were (i) presence of concomitant inflammatory rheumatic diseases, (ii) history of acute and/or chronic infections, (iii) concomitant cardiovascular disease, (iv) history of diabetes mellitus, (vi) major organ dysfunction, (vii) recent or current use of corticosteroids, antiaggregants, and/or anticoagulants, and (viii) history of malignancy or hematological disease. A total of 50 healthy age- and sex-matched volunteers were included in this study.

The Local Ethics Committee approved the study protocol (Date: September 16, 2022, Number: 125/13). Before enrolling in the study, each participant signed an informed consent form. The Declaration of Helsinki's guiding principles were followed.

Clinical parameters

Patients' demographic information (age and sex), body mass index (BMI), current smoking, alcohol use, symptom duration (years), time of diagnosis (years), presence of peripheral arthritis, duration of morning stiffness (minutes), and medications (non-steroidal anti-inflammatory drugs [NSAIDs] and biologic agents) were recorded. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP), and the Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate (ASDAS-ESR) were used to evaluate disease activity. BASDAI scores <4 and ≥4 indicated remission and active disease, respectively[15]. Regarding ASDAS-CRP and ASDAS-ESR scores, the three cutoff values of 1.3, 2.1, and 3.5 were selected to separate inactive disease, low disease activity, high disease activity, and very high disease activity, respectively[16]. The functionality of the patients was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI)[17]. The Assessment of Spondyloarthritis International Society Health Index (ASAS HI) was used to document the functional and health status of patients. The ASAS HI is composed of 17 items concerning pain, sleep, mental health, sexual functions, mobility, self-care, daily activities, and social participation. The overall ASAS HI score varies between 0 and 17, with lower scores reflecting good health condition[18].

Laboratory parameters

After 12 h of fasting, morning venous blood samples were collected using conventional techniques and analyzed in the central laboratory of the hospital. The neutrophil, lymphocyte, monocyte, and platelet counts were used to calculate the following blood cell-based indexes and ratios:

(1) NLR=neutrophil count/lymphocyte count
(2) MLR=monocyte count/lymphocyte count
(3) PLR=platelet count/lymphocyte count
(4) SII=neutrophil count×platelet count/lymphocyte count
(5) SIRI=neutrophil count×monocyte count/lymphocyte count
(6) AISI=neutrophil count×platelet count×monocyte count/lymphocyte count

Laboratory measures other than blood-cell-based indexes included ESR (mm/h), CRP (mg/L), and human leukocyte antigen-B27 (HLA-B27).

Demographic variables, smoking/alcohol use, BMI, and laboratory examination, including a complete blood count, CRP, and ESR, were registered in the healthy volunteers' group.

Statistical analyses

The sample size was calculated using the G*Power® program (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Based on the research in the literature[12,19], the sample sizes that will find the difference in the indexes to be measured in the study between the patient and control groups to be significant at 5% error and 90% power were calculated in numbers ranging from 20 (effect size: 1.052) to 47 (effect size: 0.679) per group. It was decided to conduct the study with 100 patients and 50 controls because there were no studies in the literature on some of the indexes to be used in the study, and the sample sizes in similar studies were 2 patients and 1 control.

The IBM® SPSS® (IBM Corp, Armonk, NY, USA) statistical software version 20.0 was used. The normality of the data was assessed by the Shapiro-Wilk test and related histograms. The demographic and clinical parameters were analyzed by descriptive tests. A comparative analysis of continuous variables between the patients and healthy volunteers, as well as among disease activity categories was performed by the Mann-Whitney U test. Pearson's chi-squared test was used to compare gender and smoking/alcohol status between groups. Data related to continuous variables were presented as either mean±standard deviation or median [25% (q1)–75% (q3) quartiles]. Spearman's correlation analysis was used to evaluate the relationship between laboratory parameters and clinical variables. Values were given as Spearman's rho (ρ). The p-values below 0.05 were accepted as "statistically significant".

RESULTS

Characteristics of the participants

A total of 100 patients with AS and 50 healthy individuals were included in this study. The demographic and laboratory characteristics of the study groups are shown in Table 1. Accordingly, there was no difference between groups in terms of age and gender (p=0.624 and p=0.806, respectively). As for the patient group, the median duration since diagnosis was 13 (6–20) years. The symptom duration, presence of peripheral arthritis, and duration of morning stiffness were 16 (8–22) years, 31% and 20 (5–33.75) min, respectively. The frequency of HLA-B27 positivity was 66%. Notably, 58% of the patients received biological therapy. The median values of BASDAI, ASDAS-CRP, ASDAS-ESR, BASFI, and ASAS HI scores were 4.6 (2.3–6.5), 2.9 (2.1–3.6), 2.8 (2–3.5), 3.8 (1.7–6.4), and 9 (5–12), respectively.

Table 1. Comparison of demographic, clinical, and laboratory parameters between groups.

Variables	AS patients (n = 100)	Control group (n=50)	p-value
Age (years)	45 (36.5–54)	45.5 (38–52)	0.624
Male gender	68 (68%)	33 (66%)	0.806
BMI (kg/m^2)	27.92±4.90	26.10±2.64	0.004
Current smoking	41 (41%)	23 (46%)	0.003
Current alcohol use	21 (21%)	15 (30%)	0.119
CRP (mg/L)	6.03 (3.34–10.60)	2.10 (1.54–2.50)	<0.001
ESR (mm/h)	18 (10.5–27)	6 (4–10)	<0.001
Neutrophil count (´10^9/L)	2.25±0.89	1.74±0.55	<0.001
Lymphocyte count (´10^9/L)	2.29±0.69	2.26±0.59	0.789
Monocyte count (´10^9/L)	0.61±0.19	0.49±0.14	<0.001
Platelet count (´10^9/L)	268.80±67.76	241.34±54.48	0.014
NLR (´10^9/L)	2.25±0.89	1.72±0.52	<0.001
MLR (´10^9/L)	0.28±0.09	0.22 ±0.06	<0.001
PLR (´10^9/L)	126.74±44.73	112.36±33.87	0.03
SII (´10^9/L)	603.41±287.78	418±164.75	<0.001
SIRI (´10^9/L)	1.11 (0.86–1.83)	0.77 (0.60–0.94)	<0.001
AISI (´10^9/L)	305.66 (196.80–125.97)	181.98 (125.97–259.76)	<0.001

Values are presented as n (%), median (q1-q3) or mean±standard deviation. AS: ankylosing spondylitis; BMI: Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation.

Comparative analysis of laboratory parameters between groups

The comparison of laboratory findings between patients with AS and controls are given in Table 1. Accordingly, the levels of CRP and ESR were statistically higher in the patient group ($p<0.001$ for both). In addition, neutrophil, monocyte, and platelet counts were also significantly higher in patients with AS ($p<0.001$,<0.001, and 0.014, respectively). All investigated blood cell-derived indexes were remarkably higher in patients than those in controls ($p<0.001$ for all except PLR $p=0.03$).

Comparison of laboratory findings stratified for Bath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity Score with C-reactive protein/ Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate score

When the laboratory parameters were compared between the active and remisson groups according to the BASDAI score, the ESR value was higher in the active group than in the remission group ($p=0.009$), whereas there was no significant increase in the CRP value ($p=0.150$). When the groups were compared according to ASDAS-CRP and ASDAS-ESR scores, both CRP and ESR values for both disease activity measures were significantly higher in the high-very high disease activity group compared to the inactive-low disease activity group (Table 2).

Correlation analysis of laboratory parameters with disease-related variables

The results of the correlation analysis of laboratory findings with disease-related and inflammatory parameters, including CRP and ESR, in patients with AS are displayed in Table 3. Accordingly, SII showed a weak positive correlation between ASDAS-CRP and ASDAS-ESR ($\rho=0.197$ and 0.201, respectively). However, there was no correlation between SII and BASDAI, BASFI, and ASAS HI. Other blood cell-derived indexes were not correlated with disease-related variables. PLR, SII, SIRI, and AISI, showed a weak positive correlation with CRP and ESR (ρ ranged from 0.200 to 0.381).

DISCUSSION

In this cross-sectional study, we performed an assessment of various blood cell-derived indexes to investigate the role of those in demonstrating the inflammatory burden, disease activity, functional status, and general health status in AS. Over the last decade, studies have reported the efficacy of indexes, especially in NLR, MLR, and PLR in rheumatic diseases, including AS.

Table 2. Laboratory findings of the patients with ankylosing spondylitis stratified for Bath Ankylosing Spondylitis Disease Activity IndexBath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity scores.

Variables	BASDAI score			ASDAS-CRP score			ASDAS-ESR score		
	≥4 (n=59)	<4 (n=41)	p	≥2.1 (n=76)	<2.1 (n=24)	p	≥2.1 (n=75)	<2.1 (n=25)	p
CRP (mg/L)	6.5 (3.61–12.20)	5.46 (3.17–9.08)	0.150	6.95 (3.96–11.85)	3.76 (3.52–5.10)	<0.001	6.85 (3.62–12.2)	4 (2.79–5.61)	0.004
ESR (mm/h)	21 (12–30)	15 (8–23)	0.009	21.5 (13.5–28.5)	9.5 (5.5–16)	<0.001	22 (14–29)	9 (5–14)	<0.001
NLR (´10⁹/L)	2.25±0.85	2.25±0.95	0.998	2.26±0.89	2.19±0.89	0.731	2.27±0.89	2.15±0.90	0.543
MLR (´10⁹/L)	0.28±0.09	0.28±0.1	0.837	0.29±0.09	0.26±0.09	0.314	0.29±0.09	0.27±0.09	0.340
PLR (´10⁹/L)	128.43±45.41	124.31±44.17	0.652	129.88±45.75	116.80±40.61	0.213	130.12±44.93	116.61±43.41	0.192
SII (´10⁹/L)	542.40 (391.89–838.65)	524.32 (383.68–670.72)	0.455	559.08 (388.52–780.88)	509.34 (382.83–557)	0.265	557.33 (395.31–780.92)	505.69 (359.80–556.67)	0.89
SIRI (´10⁹/L)	1.07 (0.84–1.84	1.12 (0.92–1.79)	0.911	1.11 (0.86–1.86)	1.12 (0.91–1.35)	0.651	1.17 (0.88–1.87)	1.10 (0.78–1.36)	0.306
AISI (´10⁹/L)	307.91 (195.95–503.19)	303.41 (203.82–426)	0.563	323.18 (198.59–490.21)	289.88 (176.07–384.94)	0.239	323.35 (163–367.03)	256.50 (203.82–503.19)	0.081

Values are presented as n (%), median (q1-q3) or mean±standard deviation. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate.

Table 3. Correlation of laboratory parameters with disease-related variables in patients with ankylosing spondylitis.

	CRP	ESR	BASDAI	ASDAS-CRP	ASDAS-ESR	BASFI	ASAS HI
NLR (´10⁹/L)	0.236*	0.142	0.015	0.137	0.119	0.057	-0.014
MLR (´10⁹/L)	0.179	0.160	-0.23	0.46	0.060	-0.039	-0.093
PLR (´10⁹/L)	0.265**	0.272**	-0.010	0.115	0.140	-0.016	0.003
SII (´10⁹/L)	0.381***	0.348***	0.023 0.823	0.197*	0.201*	0.029	0.027
SIRI (´10⁹/L)	0.233*	0.200*	-0.026	0.077	0.079	-0.034	-0.081
AISI (´10⁹/L)	0.364***	0.351***	0.004	0.145	0.154	-0.034	-0.002
CRP (mg/L)	–	0.672***	0.228*	0.539***	0.451***	0.324**	0.305***
ESR (mm/h)	0.672***	–	0.355***	0.556***	0.667***	0.403***	0.365***

Values represent Spearman's rho. *p<0.05, **p<0.01, ***p<0.001. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; $ASDAS_{ESR}$: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASAS HI: Assessment of Spondyloarthritis International Society Health Index.

However, the relation of SII to AS has been much less studied so far and two novel indexes, SIRI and AISI, have not yet been investigated in AS. This study revealed that SII, SIRI, and AISI were remarkably higher in patients with AS compared to healthy individuals. On the contrary, they were positively correlated with conventional systemic inflammatory markers, including CRP and ESR. These indexes may be used to indicate a chronic inflammatory state in AS. However, they had no correlation with any of the disease activity/health measures except for a very weak positive correlation of SII with ASDAS-CRP and ASDAS-ESR.

In this regard, blood cell-based indexes, including NLR, PLR, SII, SIRI, and AISI, have potential to reflect systemic inflammation in AS. However, they are not helpful in terms of the evaluation of disease activity, functional status, and general health status. The inefficiency of blood cell-derived indexes in determining disease activity and general health status can be explained in several ways. Tools like BASDAI, BASFI, and ASAS HI are solely patient-reported measures. They may not only depend on inflammation itself, but are also related to psychological status, illness perception, and sleep quality. Moreover, concomitant health conditions such as central sensitization definitely interfere with patient-reported measures of AS[20,21]. We found no correlation between patient-reported measures and blood-cell-derived indexes. Yet, ASDAS-CRP and ASDAS-ESR showed a correlation with one of these indexes (SII). This correlation could be attributed to the composite design of the ASDAS-CRP and ASDAS-ESR tools. Composite disease activity measures of AS include not only patient-reported queries but also objective markers of inflammation (CRP or ESR)[22].

A novelty of this study is related to the potential role of SIRI and AISI in defining the inflammatory status of patients with AS. To the best of our knowledge, their potential indicatory role on inflammation in AS has not been reported so far. On the contrary, we revealed potential effectiveness of SII, NLR, and PLR in reflecting inflammatory status, which had previously been demonstrated in several other studies[6-8,19]. Wu et al. reported that SII was positively correlated with CRP (r_s=0.483), ESR (r_s=0.374), and BASDAI (r_s=0.667) and also a risk factor for high disease activity in patients with AS[13]. Despite the usefulness of these indexes in determining inflammation, this study revealed that they were ineffective in the determination of disease activity and the stratification of disease severity.

One of the strengths of this study is that extensive analysis of novel indexes, SIRI and AISI, has not yet been studied in AS. The association between blood cell indexes and disease activity measures, functional status, and general health status of patients with AS has also been extensively investigated for the first time. In addition, according to the cross-sectional observational study design, the prospective collection of data from individuals enrolled in this study allowed appropriate participant selection, thereby excluding possible co-existing medical conditions that could affect these indexes. The main limitation of this study is that the study population consisted of real-life patients, and almost all received NSAIDs and/or biologics at the time of evaluation. Therefore, the impact of pharmacological therapy on these indexes could not be assessed or excluded, which might lead to confounding bias.

In conclusion, NLR, MLR, PLR, SII, SIRI, and AISI are higher in patients with AS compared to the controls, and positive

correlation exists between PLR, SII, SIRI, and AISI with CRP and ESR. Accordingly, this study provides evidence that simple, cheap, and easily calculated blood cell indexes (particularly SII, SIRI, and AISI) are reasonable measures to determine systemic inflammation in AS. On the contrary, these indexes are not effective in demonstrating disease activity, functional status, or general health status in AS.

DATA AVAILABILITY

The datasets gathered during the preparation of this article are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was approved by the Local Ethics Committee of Cukurova University Faculty of Medicine (Date of approval: September 16, 2022, Number: 125/13) and the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each study participant.

AUTHORS' CONTRIBUTIONS

AS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ICB:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **IT:** Conceptualization, Methodology, Writing – review & editing. **IU:** Conceptualization, Formal Analysis, Methodology, Software, Writing – review & editing. **SSZA:** Conceptualization, Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

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First management of percutaneous dilatational tracheostomy in severe acute respiratory syndrome coronavirus 2 akin to the vital head and neck region and thyroid gland bed: trust, but be careful whom (you trust)?

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SUMMARY

OBJECTIVE: The objective of this study was to compare the clinical outcomes of percutaneous dilatational tracheostomy in COVID-19 and non-COVID-19 patients.

METHODS: A total of 48 patients who underwent percutaneous dilatational tracheostomy, with 24 COVID-19 patients (Group C) and 24 non-COVID-19 patients (Group N), were included in the study. Patients' demographic features including age and gender, time to intubation, duration of intubation, Acute Physiology and Chronic Health Evaluation scores, comorbidities, duration of opening tracheostomy, complications, duration of mechanical ventilation, length of stay in the intensive care units, and mortality were recorded and compared between the groups.

RESULTS: There was no statistically significant difference between the groups regarding age and gender (p=0.558 and p=0.110, respectively). Time to intubation was significantly more prolonged, and intubation follow-up duration was significantly shorter in Group C compared to Group N (p=0.034 and p=0.002, respectively). The Acute Physiology and Chronic Health Evaluation score was statistically significantly higher in Group N compared with Group C (p=0.012). The most common comorbidity was hypertension in 29 (60.4%) patients, followed by cerebrovascular disease in 19 (39.6%) patients. There was no statistically significant difference between the groups regarding mortality (p=0.212).

CONCLUSION: This study suggests that percutaneous dilatational tracheostomy can be performed safely in COVID-19 and non-COVID-19 patients. However, COVID-19 patients may have a longer time to intubation and shorter intubation follow-up duration than non-COVID-19 patients. The study also found a higher incidence of complications in COVID-19 patients undergoing percutaneous dilatational tracheostomy. These results emphasize the importance of careful patient selection, meticulous technique, and close postoperative monitoring in patients undergoing percutaneous dilatational tracheostomy, particularly in those with COVID-19.

KEYWORDS: Tracheostomy. Mechanical ventilation. Intensive care. COVID-19. Complications. Thyroidology.

INTRODUCTION

Percutaneous dilatational tracheostomy (PDT) was developed by Ciaglia et al.[1] over a guidewire in 1985. Since then, many renditions of this technique have come to the forefront, but none has been as famous as the original method[2]. PDT involves blunt dissection of tissues followed by dilatation of the trachea over the guidewire and placement of the tracheal cannula[3,4]. Proponents of PDT suggest that the limited dissection results in less damage lowers the risk of bleeding and wound infection and can be performed at the bedside in the intensive care units (ICUs), which may overcome the risk associated with transporting critically ill patients[5]. PDT is indicated to protect airways in patients at risk of aspiration, in anticipated prolonged mechanical ventilator stay, to facilitate

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weaning in difficult-to-wean patients, and to minimize the need for sedation[6,7]. Complications related to the PDT procedure include bleeding, pneumothorax, incorrect cannula insertion, thyroid injury, and subcutaneous emphysema, with most of these minor complications. Absolute contraindications to PDT include cervical instability, infection at the planned insertion site, and uncontrolled coagulopathy[8-11]. The onset of the COVID-19 pandemic has resulted in an increased number of patients with severe acute respiratory distress syndrome in ICUs worldwide[12,13]. Patients with COVID-19 pneumonia often require mechanical ventilation in the ICU, and prolonged ventilation and difficulty in weaning warrant tracheostomy in these patients. With COVID-19, a new dimension has been added to the debate on the timing of PDT, given that tracheostomy can be an aerosol-generating procedure with a risk of spreading the infection to involved healthcare personnel. However, increasing evidence now suggests that the risk of a surgical team is shallow if the protective measures are carefully implemented[14-16]. To the best of our knowledge, this is the first study in the English-language literature comparing tracheostomy procedures between patients with and without COVID-19, concerning the vital head and neck region.

METHODS

Ethical aspects

This study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Giresun University, under the approval number E-90139838-000-148666.

Study design

The study population consisted of a total of 48 cases who had undergone PDT between September 2020 and January 2023, with 24 cases with and 24 without COVID-19. Patients over 18 years who had undergone PDT were included, whereas exclusion criteria were (i) under 18 years, (ii) severe hypercapnia, (iii) surgical tracheostomy, and (iv) missing data. Patients' demographic features including age, sex, time to intubation, Acute Physiology and Chronic Health Evaluation (APACHE) score, comorbidity, time for tracheostomy procedure, complication, time for mechanical ventilation, length of stay (LOS) in the ICU, and mortality were recorded and compared between the groups. The diagnosis of COVID-19 was established with the polymerase chain reaction test. The medical staff who performed tracheostomy in COVID-19 cases had used full personal protective equipment (PPE), face shield, N95 mask, and sterile surgical gloves.

Percutaneous dilatational tracheostomy procedure

The endotracheal tube replacement and oral aspiration were performed before the procedure. The patients were provided with adequate analgesia, sedation, and muscle relaxation, and the head and neck regions were then hyperextended in the supine position. The anterior cervical area was sterilized and covered, and 2 mL of the local anesthetic agent (lidocaine 20 mg+epinephrin 12.5 µg) was used before the incision of the procedure. An approximately 2 cm incision was performed between the cricoid cartilage and the suprasternal notch. Afterward, subcutaneous tissue was separated with a hemostat until the tissue surrounding the trachea was exposed. The trachea was separated from the muscles and a 5 mL syringe with a guidewire was filled with 3 mL saline. Of note, a small-diameter dilator over the guidewire widened the tracheal opening, and the skin and subcutaneous tissue were dilated at least twice with dilatation forceps. The dilatation forceps were then inserted gently into the trachea over the guidewire, and dilatation was performed. Finally, a lubricated tracheostomy cannula was placed over the guidewire and into the trachea after providing bleeding control and adequate patency. After ventilation of the patient was observed, a pressure dressing was applied, and tube fixation was performed by surgical suturing.

Statistical analysis

The data of all patients were entered into a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS, IBM Inc., Chicago, IL, USA) software. The normality of the variables was tested using the Shapiro-Wilk test. Continuous variables were expressed as mean, standard deviation, or median (25–75 percentile) according to their distribution status, and categorical variables were expressed as numbers and percentages. The independent-sample t-test was used where parametric test assumptions were met in the analysis of continuous variables; otherwise, the Mann-Whitney test was used. The chi-square or Fisher's exact test was used to analyze categorical variables, and $p<0.05$ values were considered statistically significant.

RESULTS

This retrospective study incorporated 48 patients who had undergone PDT from April 2023 to May 2023. A sum of 24 cases with COVID-19 ($wCVD_{19}$) pneumonia was assigned to Group C, while those without COVID-19 ($woCVD_{19}$) pneumonia were set to Group N. No statistically significant difference between them in terms of age and sex based

on their demographic features was recognized (p=0.558 and p=0.110, respectively). However, the time to intubation was significantly more prolonged, and the intubation follow-up duration was significantly shorter in Group C compared with Group N (p=0.034 and p=0.002, respectively). The APACHE score was statistically significantly higher in $woCVD_{19}$ compared with $wCVD_{19}$ (p=0.012) (Table 1). The most common comorbidity was hypertension in 29 (60.4%) cases, followed by CVD in 19 (39.6%). There was no statistically significant difference between the two groups in terms of comorbidities (for all, p>0.05) (Table 2). The duration of the tracheostomy procedure was statistically significantly longer in wCVD19 (p<0.001). A total of 18 cases in wCVD19 and 6 in $woCVD_{19}$ had developed complications, i.e., 3 developed pneumothorax and 12 had bleeding, while 3 had subcutaneous emphysema in $wCVD_{19}$. In comparison, two developed pneumothorax, three had bleeding, and one had subcutaneous emphysema in $woCVD_{19}$. A statistical significance between the groups based on the complication status and bleeding parameters has been recognized as the tracheostomy complications were evaluated in detail (p<0.05). Contrarily, "pneumothorax" and "subcutaneous emphysema" parameters were detected to be similar between them (p>0.05) (Table 3). The duration of mechanical ventilation and LOS in the ICU was significantly higher in $woCVD_{19}$ (p=0.001 and p=0.002, respectively). The mortality rate was 62.5% (n=15) in wCVD19, whereas it was 37.5% (n=9) in $woCVD_{19}$. However, no significant difference was noticed between them regarding discharge events (p=0.212) (Table 3).

Table 1. The intubation statuses with demographic characteristics of the cases.

Characteristic features	$wCVD_{19}$	$woCVD_{19}$	p-value
Sex, n (%)			
Male	15 (62.5%)	13 (54.2%)	0.558
Female	9 (37.5%)	11 (45.8%)	
Age (years)	61 (47–77)	76 (56–85)	0.110
Time to intubation (days)	8 (5–13)	5 (2–10.5)	0.034
Intubation follow-up (days)	14.8±6.7	20.8±6.3	0.002
APACHE score	12 (6–19)	19 (15–23)	0.012

The categorical variables were presented as n (%), while continuous variables were expressed as mean±SD or median (25–75 percentiles), The χ^2 test was used for categorical variables, while the t-test or Mann-Whitney U test was used for continuous variables.

DISCUSSION

The coronavirus disease was initiated when the Wuhan Municipal Health Commission reported 27 pneumonia cases with an unknown etiology on December 31, 2019, and Chinese scientists named this phenomenon that led to atypical pneumonia, i.e., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease, which originates from coronavirus, was named COVID-19 by the World Health Organization (WHO), on February 11, 2020, and accepted as a pandemic on March 11 which had spread quickly in more than 150 countries, has created an international public health problem.

The preliminary outcomes of this study revealed that the time to intubation was longer (8 vs. 5 days), while the duration of intubation was shorter (14.8 vs. 20.8 days) in wCVD19

Table 2. Comorbidities of the cases in accordance with the study groups.

Comorbidity		$wCVD_{19}$	$woCVD_{19}$	p-value
Hypertension, n (%)	No	10 (41.7%)	9 (37.5%)	0.768
	Yes	14 (58.3%)	15 (62.5%)	
CVD, n (%)	No	15 (62.5%)	14 (58.3%)	0.768
	Yes	9 (37.5%)	10 (41.7%)	
COPD, n (%)	No	22 (91.7%)	17 (70.8%)	0.137
	Yes	2 (8.3%)	7 (29.2%)	
DM, n (%)	No	19 (79.2%)	19 (79.2%)	1
	Yes	5 (20.8%)	5 (20.8%)	
CAD, n (%)	No	21 (87.5%)	21 (87.5%)	1
	Yes	3 (12.5%)	3 (12.5%)	
Epilepsy, n (%)	No	20 (83.3%)	18 (75.0%)	0.724
	Yes	4 (16.7%)	6 (25.0%)	

The χ^2 test or Fisher's exact test was used for categorical variables, and the categorical variables were shown as n (%). CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CAD: coronary artery disease.

Table 3. The procedures of tracheostomy with their supportive appendages.

Characteristics	Group C	Group N	p-value
Tracheostomy opening duration (min)	19.9±3.6	14.9±1.7	<0.001
Tracheostomy complication, n (%)			
No	6 (25.0%)[a]	18 (75.0%)[b]	0.006
Pneumothorax	3 (12.5%)[a]	2 (8.3%)[a]	
Bleeding	12 (50.0%)[a]	3 (12.5%)[b]	
Subcutaneous emphysema	3 (12.5%)[a]	1 (4.2%)[a]	
Mechanical ventilation duration (days)	41.3±20.7	68.2±31.6	0.001
Length of stay in the ICU (days)	50.6±24.7	79.5±34.9	0.002
Discharge, n (%)			
Other ICU	6 (25.0%)	9 (37.5%)	0.212
Mortality	15 (62.5%)	9 (37.5%)	
Ward	3 (12.5%)	6 (25.0%)	

While continuous variables were expressed as mean±SD, categorical variables were presented as n (%). The chi-square test was used for categorical variables, while the t-test was used for continuous variables. Each same superscript (a, b) denotes a subset of group categories that are not statistically significantly different from each other at the p=0.05 level.

compared with woCVD19. In a study by Tang et al.[16], the intubation time was 17.5 days in wCVD19. Similar to our study, some authors reported that the duration from intubation to tracheostomy was 15.24 days in woCVD19. In addition, we declared that the median APACHE II score was 12 in wCVD19, while it was 19 in woCVD19, and the APACHE score was significantly lower in wCVD19 (p=0.012). In the study by Koc, the median APACHE II score was 32.35 in $woCVD_{19}$[17]. Different study results might be due to diverse patient populations and methodology.

The incidence of comorbidities increases with aging. In our study, the most common comorbidity was hypertension, followed by CVD. The other comorbidities included chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, and epilepsy. In a study by Battaglini et al. with $wCVD_{19}$ undergoing tracheostomy, the most common comorbidity was hypertension, followed by diabetes mellitus and chronic cardiac disease[18]. Our result was similar to the previous studies. The mean duration of mechanical ventilation was 41.3 days in $wCVD_{19}$ and 68.2 days in $woCVD_{19}$, while in a study by Mahmood et al.[19] with 118 $wCVD_{19}$ undergoing tracheostomy, the median duration of mechanical ventilation was 36 days. Different results among the studies were attributed to differences in patient populations.

In this study, the mean LOS in the ICU was 50.6 in $wCVD_{19}$ and 79.5 in $woCVD_{19}$. Similarly, in a study by Koc et al.[17] with $woCVD_{19}$, the mean LOS in the ICU was found as 53.5 days, while in a study by Battaglani et al.[18] with $wCVD_{19}$ receiving PDT, the median LOS was reported as 30 days. Minimizing complications of endotracheal intubation and mechanical ventilation in the ICU is essential. These complications should be detected quickly, and necessary surgical intervention should be performed through neck exploration without delay. PDT is preferred in prolonged intubation cases to ensure the patients' airway safety and comfort. PDT is preferred for its advantages, including low complication rates and short opening time[20]. In this study, the most common complications of PDT were pneumothorax, bleeding, and subcutaneous emphysema[21], while in a study by Battaglani et al.[18], the most common complications were bleeding, stoma infection, and pneumothorax. In a study by Mahmood et al.[19], the most common complications in $wCVD_{19}$ receiving tracheostomy included bleeding, dislodgement of tracheostomy, and pneumothorax.

The mortality rate of this study was 62.5% in $wCVD_{19}$ and 37.5% in $woCVD_{19}$. There was no significant difference between the patients in terms of mortality, while in a study by Mahmood et al.[19], the mortality rate in $woCVD_{19}$ receiving PDT was 15.2%. Our higher mortality rate in $wCVD_{19}$ was attributed to the relatively small number of patients.

Study limitations

The main limitations of this study include the small number of patients and is conducted as a retrospective study in a single center. In addition, early and late PDT could not be examined separately. On the contrary, the strength is that this is the first study in the literature comparing the PDT procedure between $woCVD_{19}$ and $woCVD_{19}$ undergoing PDT.

CONCLUSION

Our study provides important insights into the safety and efficacy of PDT in $wCVD_{19}$ and $woCVD_{19}$. We recommend that clinicians follow the guidelines for tracheostomy in $wCVD_{19}$, including appropriate PPE and a multidisciplinary approach. Future studies with larger sample sizes are needed to confirm our findings and optimize the management of critically ill patients requiring tracheostomy during the COVID-19 pandemic. In summary, our study adds to the growing body of evidence on managing $wCVD_{19}$ and underscores the importance of continued research to improve patient outcomes in this challenging population.

AUTHORS' CONTRIBUTIONS

TA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **HY:** Investigation, Methodology, Project administration, Validation, Visualization. **DS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **IS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – review & editing. **MA:** Investigation, Validation, Visualization. **SE:** Investigation, Validation, Visualization. **AM:** Investigation, Validation, Visualization. **EC:** Investigation, Validation, Visualization.

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ORIGINAL ARTICLE

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Pain sensitization and atrophy of deep cervical muscles in patients with chronic tension-type headache

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SUMMARY

OBJECTIVE: The aim of this study was to compare the pressure pain threshold and the thickness of the cervical muscles in patients with tension-type headache versus healthy participants.

METHODS: An observational, retrospective, cross-sectional study was conducted at the Universidad Europea de Madrid between May and June 2022. Adults aged 18–65 years with tension-type headache diagnosed for more than 6 months were compared to healthy controls. B-mode ultrasound imaging was employed to measure the thickness of the neck stabilizing muscles, longus colli, and multifidus at the C5 and C6 levels, respectively. pressure pain threshold measurements were assessed bilaterally in the following regions: upper trapezius, masseter, temporalis, anterior tibialis, and median nerve.

RESULTS: A total of 40 participants (90% females; 36.3±12.9 years, BMI 24.2±3.7 kg/m^2) participated in the study. Compared with the control group (n=20), participants in the tension-type headache group (n=20) presented statistically significant lower values in all pressure pain threshold measures. Additionally, the tension-type headache group presented statistically significant lower values in the thickness of the following muscles: right multifidus at rest (1.0±0.2 cm versus 1.3±0.2 cm; p<0.001), left multifidus at rest (1.1±0.1 cm versus 1.3±0.1 cm; p<0.001) and during contraction (1.2±0.1 cm versus 1.5±0.2 cm; p<0.001), left longus colli at rest (1.0±0.2 cm versus 1.2±0.1 cm; p=0.01) and during contraction (1.2±0.2 cm versus 1.4±0.1 cm; p<0.001), and right longus colli during contraction (1.2±0.2 cm versus 1.4±0.2 cm; p=0.02).

CONCLUSION: This study concluded that patients with tension-type headache showed lower thickness and lower pressure pain threshold of cervical muscles compared to healthy controls.

KEYWORDS: Neck pain. Neck muscles. Tension type headache. Muscle atrophy.

INTRODUCTION

Tension-type headache (TTH) is the most prevalent type of headache, affecting 36–78% of adults[1]. It shares similarities with migraines, occurring in both episodic and chronic forms[2]. Both TTH and migraines are more common in females, with a ratio of 3:1 compared to males[3].

The association between cervical pathology and headaches appears to be linked to the convergence of nociceptive input from the upper cervical spine and trigeminal input at the trigeminal-cervical nucleus level[4]. This convergence justifies the ability to reproduce headaches by applying pressure to cervical structures[5] and the sensitization of areas innervated by the trigeminal-cervical nucleus. This sensitization can be measured using algometry, which has shown reduced values in the craniocervical region. Patients with TTH have greater pressure sensitivity in craniocervical muscles such as the upper trapezius, suboccipital, temporalis, and masseter muscles, compared to healthy subjects[6].

In addition, some studies have observed reduced pressure sensitivity in remote areas from the cervical region, such as the tibialis anterior muscle, in patients with TTH[7], suggesting a process of central sensitization that is more pronounced in females.

Muscle pain, loss of strength, and lower motor control seem to be correlated in patients with TTH[8]. Consequently, it is conceivable that the loss of strength may be associated with changes in the thickness of cervical muscles, but the results are not clear[9]. The conflicting results and the generally low methodological quality of the existing studies on this topic prevent definitive conclusions from being drawn.

Therefore, the aim of this study was to analyze the pressure pain threshold (PPT) and the thickness of cervical muscles at rest and during contraction in patients with TTH.

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METHODS

Study design and ethical considerations

An observational, cross-sectional study was conducted at the Universidad Europea de Madrid following the STROBE guidelines between May and June 2022. This study followed the Declaration of Helsinki guidelines. The study was approved by the Research Ethics Committee of the Rey Juan Carlos University of Madrid (ID: 1802202105721). All the participants read and signed an informed consent statement before participating in this investigation.

Participants

The participants for this study were recruited from students and workers at the Universidad Europea de Madrid (Spain), who were included in the study if they fulfilled the following criteria: (1) adults aged 18–65 years and (2) diagnosis of TTH for more than 6 months, confirmed by their neurologist, using the criteria of the International Headache Society classification of headaches (ICHD-3). The most significant finding was increased tenderness in pericraneal muscles such as masseter, temporal, and upper trapezius.

Inclusion criterion for controls was the absence of headache. Exclusion criteria were as follows: (1) the presence of pathologies that prevent the performance of physical activity; (2) pregnancy; (3) concomitant severe respiratory, cardiovascular, or neurological disease; and (4) previous whiplash injury or neck fracture. Participants with TTH were matched with their controls by age, sex, and body mass index (BMI).

Sample size

The sample size calculation was realized using the G*Power 3.1.9 software (G*Power ©, University of Dusseldorf, Düsseldorf, Germany). A two-tailed hypothesis with an effect size of 0.81, an alpha error of 0.05, a statistical power of 0.8, and an allocation ratio of 1 were performed. Therefore, the total sample size was 40 participants, who were divided into two groups (n=20): the TTH group and the control group.

Measurements

First, the following anthropometric variables were collected: age in years, height in centimeters (cm), weight in kilograms (kg), and BMI (kg/m^2).

Then, the characteristics of headache episodes were assessed. The duration of headaches was measured in hours, the intensity on the numerical pain rating scale ranged from 0 (no pain) to 10 (maximum pain), and the frequency of the episodes was measured in days[10].

Next, to measure the PPT, a FORCE DIAL FDK/FDN 100 algometer (Wagner Instruments, Greenwich, USA) was used as the measurement tool. PPT is known to be the most validated mechanical threshold at present[11]. Patients were taught to be familiarized with the procedure by testing it in a non-involved area in the study (vastus medialis). The procedure was repeated three times with a resting period of 30 s between repetitions. Patients were instructed to report when pain appeared while exerting pressure with the algometry device, that is, the first pain signal. Pressure was applied progressively at a smooth pace of 1 kg/s. The average was calculated from all repetitions. Participants were assessed while laying supine on a stretcher by a physiotherapist. PPT measurements were performed bilaterally in the following regions: trapezius, masseter, temporalis, anterior tibialis, and median nerve in the flexion crease of the elbow, in order to determine if low values over these spots in headache participants could determine a relation between headache and central and peripheral mechanical pain sensitivity[12]. Intraclass correlation coefficients were considerably high (ICC: 0.83–0.89). In addition, intraexaminer (ICC=0.94–0.97) and interexaminer reliability (ICC=0.79–0.90) were elevated[13].

Finally, the thickness of the neck stabilizing muscles, multifidus, and flexor longus colli was measured at the cervical C5 and C6 levels, respectively. It was assessed by using ultrasonography (GES7, GE Healthcare, Chicago, USA) both at rest and during counter-resistance, following the methodology of Øverås and collaborators[14]. Participants laid in a supine position for flexor longus colli and prone for multifidus assessments. Counter-resistance contraction was performed by instructing the participant to reproduce a double-chin command in case of flexor longus colli, and isometric neck extension to evaluate multifidus. Contraction was maintained for 3 s. The procedure was repeated three times with a resting period of 30 s between repetitions, and the average measurement was calculated and recorded. Inter-rater reliability of thickness during contraction was found to be good for longus colli muscles and moderate-to-low for multifidus.

Statistical analysis

Shapiro-Wilk test was performed to observe whether the distribution was parametric or non-parametric for all variables. Then, independent samples t-test was performed to determine whether there were significant differences between the TTH group and the control group in all parametric variables. The Mann-Whitney U test was performed for the non-parametric variables. For the categorical variable (sex), an exact Fisher's test was performed. The significance level was set at

alpha <0.05. All analyses were performed using the SPSS 27.0 (IBM) statistical software.

RESULTS

Sociodemographic data

A total of 40 participants (36 females, 90%) with a mean age of 36.3±12.9 years, a height of 165.11±10.65 cm, a weight of 66.1±11.1 kg, and a BMI of 24.2±3.7 kg/m^2 participated in the study, with no significant differences in these variables between the TTH group (n=20) and the control group (n=20) (Table 1).

Pain characteristics

The TTH group had headache episodes with a mean frequency of 11.1±9.5 days per month, a pain intensity of 6.9±1.7 (on a scale of 0 to 10), and a duration of episodes of 10.4±8.9 h.

Pain pressure threshold

The TTH group presented statistically significant lower values in all PPT measures compared with the control group, i.e., in left temporalis (p<0.001), right temporalis (p<0.001), left upper trapezius (p<0.001), right upper trapezius (p<0.001), left masseter (p<0.001), right masseter (p<0.001), left median nerve (p<0.001), right median nerve (p<0.001), left anterior tibialis (p<0.001), and right anterior tibialis (p<0.001) (Table 2).

Ultrasound thickness

The THG presented statistically significant lower values in the thickness of the following muscles: right multifidus at rest (p<0.001), left multifidus at rest and during contraction (p<0.001), left flexor longus colli at rest (p=0.01) and during contraction (p<0.001), and right flexor longus colli during contraction (p=0.02). No significant differences were detected in the thickness of the right multifidus during contraction or in the right flexor longus colli at rest (Table 3).

Table 1. Sociodemographic data of the tension-type headache group and control group.

Variables	TTH group (n=20)	Control group (n=20)	p-value
Sex (male/female)	2/18	2/18	n.s
Age (years)	37.5±13.1	35.9±12.2	n.s
Height (cm)	166.12±11.09	164.98±10.02	n.s
Weight (kg)	67.88±12.08	65.8±10.90	n.s
BMI (kg/m^2)	24.38±3.80	24.11±3.98	n.s

Data are presented as mean±standard deviation or n (sex). n.s: non-significant.

DISCUSSION

This study compared the PPT and the thickness of the cervical muscles in patients with TTH compared to healthy participants. The PPT in the upper fibers of the trapezius, masseter muscle, temporal muscle, tibialis anterior muscle, and median nerve were lower in participants with TTH compared with controls. In addition, the thickness of the cervical muscles (multifidus and longus colli) of the TTH group at rest and during contraction was lower compared with the control group.

Table 2. Pain pressure threshold of the participants.

Variables	TTH group (n= 20)	Control group (n=20)	p-value
PPT temporalis R (kg/cm^2)	3.0±1.0	5.6±0.5	<0.001*
PPT temporalis L (kg/cm^2)	2.9±1.1	5.6±0.4	<0.001*
PPT upper trapezius R (kg/cm^2)	3.5±1.6	6.5±0.7	<0.001*
PPT upper trapezius L (kg/cm^2)	3.5±1.6	6.6±0.7	<0.001*
PPT masseter R (kg/cm^2)	2.4±1.0	4.5±0.5	<0.001*
PPT masseter L (kg/cm^2)	2.3±0.9	4.4±0.5	<0.001*
PPT median nerve R (kg/cm^2)	3.6±1.4	6.0±0.7	<0.001*
PPT median nerve L (kg/cm^2)	3.5±1.2	6.1±0.7	<0.001*
PPT tibialis anterior R (kg/cm^2)	6.3±1.3	10.2±1.0	<0.001*
PPT tibialis anterior L (kg/cm^2)	6.5±1.7	10.1±0.9	<0.001*

L: left; R: right. *Level of significance: p<0.05. Data are presented as mean±standard deviation.

Table 3. Thickness of the cervical multifidus (C5) and longus coli.

Thickness	TTH group (n=20)	Control group (n=20)	p-value
R multifidus (cm)	1.0±0.2	1.3±0.2	<0.001*
R multifidus cont (cm)	1.2±0.2	1.5±0.2	0.07
L multifidus (cm)	1.1±0.1	1.3±0.1	<0.001*
L multifidus cont (cm)	1.2±0.1	1.5±0.2	<0.001*
R longus colli (cm)	1.0±0.2	1.1±0.1	0.2
R longus colli cont (cm)	1.2±0.2	1.4±0.2	0.02*
L longus colli (cm)	1.0±0.2	1.2±0.1	0.01*
L longus colli cont (cm)	1.2±0.2	1.4±0.1	<0.001*

R: right; L: left; cont, contracted. *Level of significance: p<0.05. Data are presented as mean±standard deviation.

Several studies have shown the relationship between anterior/posterior craniocervical muscular atrophy and neck pain or cervicogenic headache[15]. The results observed in this study show that people with TTH present a decrease in muscle thickness/atrophy in the multifidus and longus colli muscles. These findings could be associated with a decrease in cervical muscle strength, as described in the study conducted by Madsen et al.[16], where they found lower levels of strength in the extensor and cervical flexor muscles in participants with TTH compared to healthy controls. Similarly, some studies[17] have shown that a flexor muscle strengthening program managed to reduce pressure pain in patients with TTH.

In addition to the differences in the thickness of the cervical musculature, this study also observed a decrease in PPT in (i) craniocervical region, including upper fibers of the trapezius, masseter muscle, and temporalis muscle; and (ii) extra-craniocervical region, including anterior tibialis muscle and median nerve. PPT determined by algometry is a valid and reliable method for measuring craniocervical muscles[18].

Pain perception studies that evaluated the muscle sensitivity in patients with headache have clarified the pathophysiological mechanisms. It is now accepted that peripheral and central sensitization phenomena play an important role in the onset and maintenance of tension headache[18]. According to this model that tries to explain the pathophysiology of TTH, central sensitization could be the reason why episodic TTH can become chronic because a constant sending of nociceptive stimuli from cervical structures can cause the activation of second-order neurons at the level of the trigeminal caudais nucleus.

The PPT represents the sensitivity of the tissues and can be performed in the craniocervical and/or extra-craniocervical regions. Depending on where these thresholds are decreased, it can be assumed that they reflect signs of sensitization of the trigeminal-cervical nucleus caudalis[19,20]. This neurophysiological model of the trigeminal-cervical nucleus caudalis may explain the appearance and maintenance of tension headaches[21,22].

Therefore, the results of this study support this neurophysiological model since the participants had a TTH lasting more than 6 months. This may explain the differences that have been observed in the PPT of the different points measured, such as extra-craniocervical structures (anterior tibialis and median nerve).

Some limitations associated with this study should be acknowledged. First, the PPT in the suboccipital muscles or levator scapulae was not measured. Only the C5 cervical segment was measured to determine the thickness of cervical multifidus. Finally, it would be interesting for future studies to determine the relationship between the intensity and frequency of episodes with muscular atrophy and the PPT.

In addition, future randomized controlled trials should include a specific neck muscle strengthening program to reduce the associated symptoms in the craniocervical region, along with pain education to reduce the chronicity of these pathologies.

CONCLUSION

This study found that patients with TTH had lower PPT in both craniocervical and extra-craniocervical points, suggesting pain sensitization compared to healthy participants. Moreover, these patients with TTH showed an atrophy of the anterior and posterior deep cervical musculature.

ETHICAL CONSIDERATIONS

This study followed the Declaration of Helsinki guidelines at all times. All the participants read and signed an informed consent statement before participating in this investigation. The study protocol was approved by the Research Ethics Committee of the Rey Juan Carlos University of Madrid on March 31, 2021 (reference number: 1802202105721).

AUTHORS' CONTRIBUTIONS

JABM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft. **AGF:** Data curation, Formal Analysis, Writing – original draft. **DDB:** Conceptualization, Data curation, Writing – original draft. **DMV:** Data curation, Formal Analysis, Methodology. **ASS:** Conceptualization, Data curation, Methodology. **GGPS:** Formal Analysis, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Performance of ChatGPT-4 in answering questions from the Brazilian National Examination for Medical Degree Revalidation

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the performance of ChatGPT-4.0 in answering the 2022 Brazilian National Examination for Medical Degree Revalidation (Revalida) and as a tool to provide feedback on the quality of the examination.

METHODS: A total of two independent physicians entered all examination questions into ChatGPT-4.0. After comparing the outputs with the test solutions, they classified the large language model answers as adequate, inadequate, or indeterminate. In cases of disagreement, they adjudicated and achieved a consensus decision on the ChatGPT accuracy. The performance across medical themes and nullified questions was compared using chi-square statistical analysis.

RESULTS: In the Revalida examination, ChatGPT-4.0 answered 71 (87.7%) questions correctly and 10 (12.3%) incorrectly. There was no statistically significant difference in the proportions of correct answers among different medical themes (p=0.4886). The artificial intelligence model had a lower accuracy of 71.4% in nullified questions, with no statistical difference (p=0.241) between non-nullified and nullified groups.

CONCLUSION: ChatGPT-4.0 showed satisfactory performance for the 2022 Brazilian National Examination for Medical Degree Revalidation. The large language model exhibited worse performance on subjective questions and public healthcare themes. The results of this study suggested that the overall quality of the Revalida examination questions is satisfactory and corroborates the nullified questions.

KEYWORDS: Artificial intelligence. Natural language processing. Education.

INTRODUCTION

Large language models (LLMs) are deep-learning algorithms capable of processing and generating text data[1]. ChatGPT (OpenAI, San Francisco, CA, USA) is one of the most recognized examples of a LLM and has gained attention for its advanced natural language processing and content-generating capabilities[2-4]. Within 2 months after its release, ChatGPT quickly became the fastest-growing consumer application, with 100 million users[5]. The ChatGPT system is user-friendly, partially free, and can interact with users on a wide range of topics[4]. As this disruptive technology is likely to have a significant and profound impact on various sectors, including healthcare, academic publishing, and medical education, it is crucial that we undertake a comprehensive assessment of its accuracy and reliability, particularly in the field of healthcare[6-8].

The Brazilian government uses a specific examination, i.e., the National Examination for Revalidation of Medical Diplomas Issued by Foreign Higher Education Institutions ("Revalida"), to validate the training of foreign physicians seeking to practice medicine in Brazil. In the 2022/2 Revalida, a total of 7,006 candidates participated in the first stage, which consisted of objective and essay-based questions. Out of these, 893 candidates advanced to the second stage, which encompassed the practical component. Ultimately, only 263 candidates passed the examination[9].

This study assessed the performance of ChatGPT-4.0 in the Brazilian National Examination for Medical Degree Revalidation and as a tool to provide feedback on the quality of the examination.

METHODS

Language model and data source

ChatGPT powered by GPT version 4.0 (GPT-4) was used because it offers a larger training set that includes a wider variety

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of sources than the previous GPT model. Moreover, GPT-4 is expected to be more reliable, creative, and able to handle more nuanced instructions, which would enable more efficient and accurate information processing[3].

The examination data were collected from the 2,022 second-semester Revalida examinations, which are publicly available on the Brazilian government website[9]. The test is organized by the Educational Research and Studies National Institute (INEP) and is composed of two distinct sections: 100 theoretical multiple-choice questions (20 each in the areas of Internal Medicine, Surgery, Pediatrics, Preventive Medicine, and Gynecology and Obstetrics) and 15 discursive questions (4 in Internal Medicine, 2 in Surgery, 4 in Pediatrics, 3 in Preventive Medicine, and 2 in Gynecology and Obstetrics). Additionally, there is a clinical skills test carried out using the Objective Structured Clinical Examination model with 10 stations. After an appeal request, the wrong and dubious questions were nullified by the INEP.

In this analysis, we included all objective questions from the theoretical section and divided them into non-nullified and nullified questions. We excluded discursive and image-based questions, as well as the practical test.

Encoding

The questions were organized according to medical themes in the following subgroups: Preventive Medicine, Gynecology and Obstetrics, Surgery, Internal Medicine, and Pediatrics. The questions were converted to plain text, and the input in the GPT-4 was in Portuguese. Multiple-choice questions were entered in full without forced justification. To reduce the memory retention bias, a new chat session was started in ChatGPT for each entry.

Adjudication

A total of two physicians (MG and RM) independently submitted all the questions and scored them for accuracy. The accuracy of objective answers was evaluated by comparing them with the examination key and classifying the responses as adequate, inadequate, or indeterminate.

The responses were considered adequate when the final answer was aligned with the responses. Inadequate answers were defined as instances in which an incorrect answer was chosen. Responses were deemed indeterminate when the answer was not present in the set of available options or there were insufficient data to provide a confident answer.

After individual evaluations, the physicians performed a third assessment to reach a consensus on the questions with differing results. The accuracy of the responses that the ChatGPT-4 presented to questions that included mathematical concepts was also included. Figure 1 shows a diagrammatic summary of the study protocol.

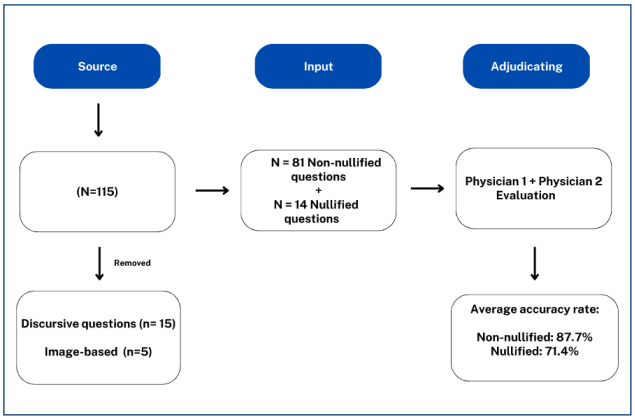

Figure 1. Workflow for sourcing, encoding, and adjudicating results.

Statistical analysis

The statistical analysis performed using Fisher's exact test compared the LLM performance across the test themes due to small sample sizes and chi-square between non-nullified and nullified questions. A two-sided test was used with a statistical significance level of α=0.05, and statistical analysis was performed using Python 3.9 libraries.

Incorrect answers were described and analyzed to evaluate the model's performance, aiming to investigate possible biases, limitations, or algorithm hallucinations.

The responses generated by ChatGPT for non-nullified questions were assessed based on the official final answer key provided by INEP. For nullified questions, the evaluation was based on the preliminary answer key provided.

RESULTS

A total of 81 objective questions were included for evaluation. Notably, 14 nullified questions were evaluated separately to analyze the reasons for their exclusion from the examination, and five image-based questions were excluded because, as a language model, ChatGPT is not designed to analyze visual content. The evaluators agreed on 72 (88.89%) of the answers and disagreed on 9 (11.11%), with no answer classified as indeterminate by both evaluators. In the settled results, the ChatGPT answered 71 (87.7%) questions correctly, 10 (12.3%) incorrectly, and there was no indeterminate answer.

Test themes

A comparison of ChatGPT-4 results through different medical themes showed the following performance: Internal Medicine 100%, Gynecology and Obstetrics 88.9%, Surgery 85.7%, Pediatrics 83.3%, and Preventive Medicine 81.3%. There was no statistically significant difference in the proportions of

correct answers among different medical themes (p=0.241). The comparison within groups is described in Figure 2.

Incorrect answers

ChatGPT answered two Gynecology and Obstetrics questions incorrectly, one about medical conduct regarding hemorrhagic shock secondary to spontaneous abortion and the other regarding the ethics of prescribing the morning-after pill. ChatGPT answered three Pediatrics questions incorrectly, which included gestational age neonates with respiratory discomfort, a neonatal dermatologic lesion, and an inguinal hernia. ChatGPT also answered three Preventive Medicine questions incorrectly, which included the approach for educating the population on the importance of COVID vaccines, the prescription of contraceptive methods, and violence against women, all of which required ethical considerations. Finally, ChatGPT answered two surgery questions incorrectly, one relating to a thyroid lesion and the other involving a clinical case.

Nullified questions

Of the 14 nullified questions, ChatGPT had an accuracy of 71.4% (n=10), with no indeterminate answers. There was no significant statistical difference in the performance of ChatGPT with non-nullified and nullified questions (p=0.240). The nullified questions comprised Gynecology and Obstetrics (n=2), Internal Medicine (n=4), Pediatrics (n=2), Surgery (n=3), and Preventive Medicine (n=3), including topics such as prescription of contraceptives, human papillomavirus screening, dyslipidemia, *Helicobacter pylori* infection and bulimia treatment, acute intoxication, neonatal syphilis, breastfeeding, cholelithiasis, trauma, recommendations against COVID-19, high-risk prenatal care, and hypertension treatment.

DISCUSSION

In this study, ChatGPT-4.0 had an overall accuracy of 87.7% in the non-nullified questions and 71.4% in the nullified questions, which corroborated the low quality of the excluded questions. Potential reasons for nullification may include ambiguity, insufficient clarity, or the presence of multiple valid answers. The evaluation comprises the objective questions of the test, excluding image-based and discursive questions.

Several articles have examined the performance of ChatGPT in the domain of general medical content[10,11]. Notably, GPT-4 demonstrated impressive performance by successfully passing Japanese medical licensing exams from 2018 to 2022[10]. Furthermore, Kung and collaborators conducted a separate study that highlighted ChatGPT's capability to pass the United States Medical Licensing Examination without any human intervention[11]. Regarding open-ended questions, ChatGPT

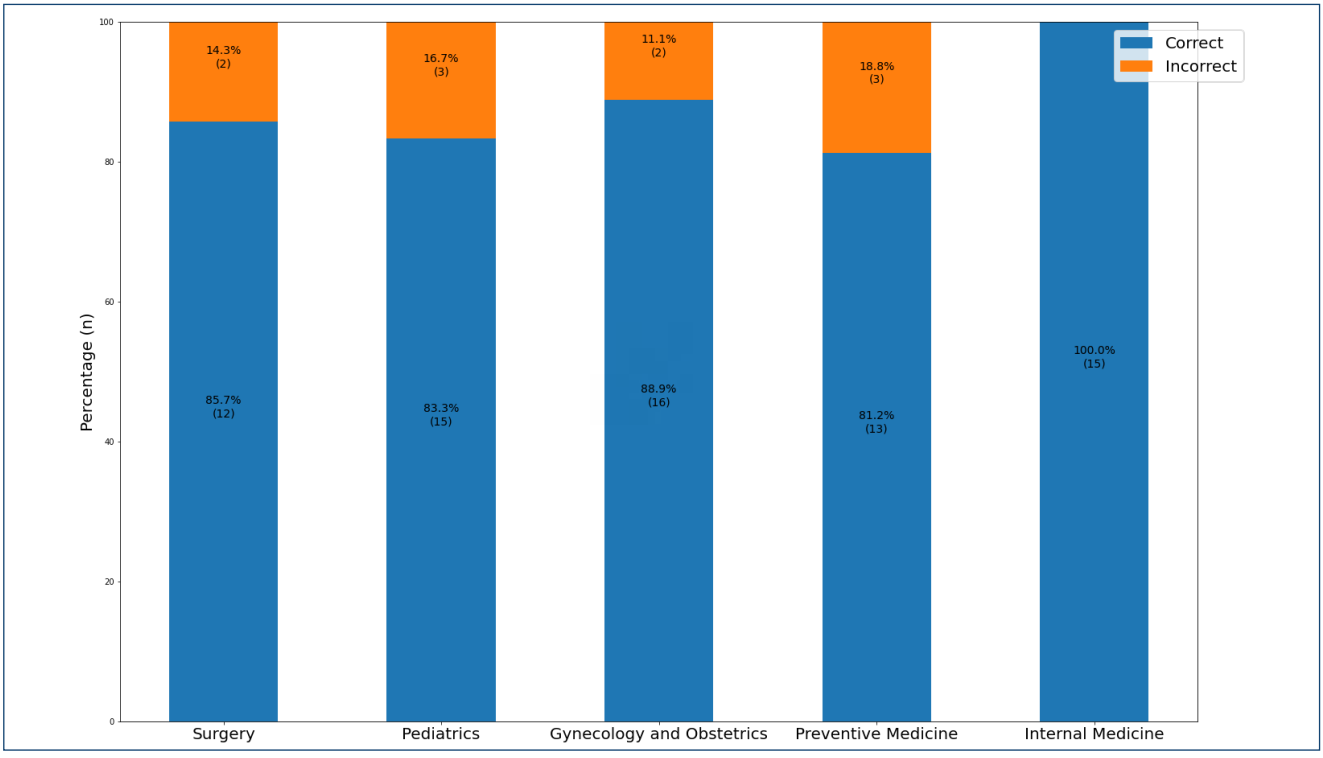

Figure 2. Performance across different examination topics.

achieved accuracies of 75.0%, 61.5%, and 68.8% for USMLE Steps 1, 2CK, and 3, respectively[11].

More recently, Belfort et al. and Mihalache evaluated the performance of ChatGPT-3.5 in answering specialist-level ophthalmology questions and found a low accuracy rate of 40.2% in the Brazilian Board exam and 46% in the American OphtoQuestions[12,13]. On the contrary, in a study conducted by the NUS Obgyn-AI Collaborative Group, ChatGPT outperformed human candidates in a Virtual Objective Structured Clinical Examination (OSCE) in Obstetrics and Gynecology. The average ChatGPT score was 77.2%, while the average historical human score was 73.7%[14].

It is important to emphasize that the evaluation of the ChatGPT-4.0's responses by two physicians allowed for a more rigorous and accurate analysis of the information provided, which contributed to a higher level of reliability when evaluating the results. The subjectivity of medical questions was also a factor to be considered, as there is often no single or correct answer for certain clinical cases, which can generate different interpretations and opinions among experts.

Comparing the medical themes, there was a discrepancy in the accuracy of the responses, with variations ranging from 100 to 81.3%, but with no statistical difference within groups due to the small sample sizes. Different question characteristics, such as clarify and less ambiguity in some themes, may have contributed to the varying performances. ChatGPT encountered challenges when responding to subjective questions within the Preventive Medicine section, which involved specific concepts related to the Brazilian public healthcare system and ethical decisions. In addition, ChatGPT did not cover information from 2022, which was related to recently issued guidelines, and included the COVID-19 pandemic. This may account for the lower accuracy in the Preventive Medicine subject area.

The results of this study show acceptable ChatGPT performance compared to results from other tests. However, the published studies used different methodologies and evaluated different examinations, making it difficult to compare the results[10-14]. The significant discrepancy between the results may be associated with the fact that the Revalida examination involves general medical topics. Another consideration is that we used the ChatGPT 4.0 version, which may have a positive impact on the results.

The Revalida examination does not include mathematical questions for evaluation. It is noteworthy that ChatGPT typically does not perform well on numerical problem-solving tasks, as previous studies reported, and may present different performances according to the language used[15].

It is essential to conduct additional and comprehensive research to investigate the underlying factors behind the low approval rate in the Revalida examination and to consider aspects such as the quality of medical education, candidate preparation, effectiveness of evaluation methods, and potential socioeconomic and cultural barriers that may affect the performance of participants[9].

LLMs are straightforward in the decision-making process and struggle with dubious and uncertain questions. The results of this study suggest that the overall quality of the Revalida examination questions is satisfactory and corroborates the annulled questions. In light of these findings, it is crucial for the medical community to recognize the potential of artificial intelligence tools such as ChatGPT-4.0 while also acknowledging their limitations. Further research is necessary to enhance the accuracy and reliability of artificial intelligence in medical education.

In conclusion, ChatGPT-4.0 performed satisfactorily at the 2022 Brazilian National Examination for Medical Degree Revalidation. The LLM exhibited a worse performance in subjective questions, public healthcare themes, and nullified questions.

AUTHORS' CONTRIBUTIONS

MG: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **LFN:** Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **RM:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **EA:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **PA:** Validation. **CVSR:** Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **RBJ:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Prevention of catheter-related bloodstream infections in patients with extracorporeal membrane oxygenation: a literature review

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INTRODUCTION

Intravenous catheters are the most common cause of bacteremia among healthcare-related infections (HCRIs)[1,2]. Intravenous catheters are most commonly used in intensive care units (ICUs). Catheter-related bloodstream infections (CRBSIs) in ICUs increase the length of stay, morbidity, mortality, and healthcare costs[3]. Extracorporeal membrane oxygenation (ECMO), which consists of invasive cannulas, is a type of extracorporeal life support (ECLS)[4]. It is used to manage the symptoms of patients with severe but reversible cardiac and/or pulmonary dysfunction. It is also sometimes used as a bridge to heart/lung transplantation[5]. It was first used in the 1950s in pediatric patients with severe cardiorespiratory failure. However, it has been widely used in adults when it resulted in increased 6-month survival in adults with severe acute respiratory distress syndrome (ARDS) during the H1N1 compared with conventional ventilation support[6]. ECMO was used in COVID patients who developed ARDS, and the reported survival rate was 33.3%[7].

ECMO is a simple cardiopulmonary bypass system that suctions venous deoxygenated blood from a large central vein through a venous cannula (16–29 Fr), oxygenates, and then restitutes it into the arterial or venous system [cannulas (20–29 Fr)] via a centrifugal pump[8]. According to the Extracorporeal Life Support Organization (ELSO), 176,496 patients underwent ECMO/ECLS support in 2021 for cardiac, respiratory, and resuscitation purposes, with a survival rate of 54%[9]. Although ECMO improves survival rates, it also causes infections that increase morbidity and mortality.

Pathogenesis

The ECMO circuit and multiple invasive interventions disrupt the skin's protective barrier, resulting in several potential entry points for pathogenic microorganisms[10,11]. ECMO patients need central venous catheters for vasoactive drugs and arterial catheters for hemodynamic monitoring. Mechanical ventilation support, urinary catheters, abdominal or chest drainage tubes, large and wide cannulas, and membrane oxygenators increase the susceptibility to nosocomial infections[12]. HCRIs increase mortality by 38–63% in ECMO patients and negatively affect the duration of ECMO support, frequency of other complications, hospitalization length, ventilator support duration, and healthcare costs[13,14]. HCRIs in ECMO patients are defined as the development of infection 24–48 h after ECMO cannulation or 48–72 h after ECMO decannulation[15].

Catheter-related bloodstream infections in extracorporeal membrane oxygenation support

Intravenous catheters are administered to millions of patients every day, leading to an increased incidence of CRBSIs[1,3]. CRBSIs are the most common HCRIs in ECMO patients. They are associated with a mortality rate of about 25%, which is 50% in critically ill patients with cardiovascular diseases[16,17]. Sun et al. reported that 7 out of 10 patients who underwent ECMO support for longer than 10 days developed CRBSIs[18]. The risk factors for CRBSIs are extended ECMO support (250 h or more), renal failure, immunosuppression, veno-arterial ECMO, and bleeding, requiring more than 1,000 mL red blood cell transfusion[19,20]. This risk is prevalent in pediatric ECMO support for longer than 5 days[21,22]. Kutleša et al. reported that ECMO support longer than 250 h and significant bleeding episodes were independent risk factors for CRBSIs[23].

Gram-negative bacteria (44.1%), gram-positive bacteria (26.5%), and fungi (29.4%) are pathogenic agents. The strains that cause bacteremia are coagulase-negative staphylococci (17.6%), *Klebsiell*a (14.7%), *Pseudomonas* (8.8%), *Acinetobacter* (8.8%), *Stenotrophomonas maltophilia* (5.9%), *Staphylococcus aureus* (2.9%), *Micrococcus* (2.9%), *Corynebacterium bovis*

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(2.9%), *Enterobacter cloaca* (2.9%), *Escherichia coli* (2.9%), *Candida Albicans,* and *Candida parapsilosis*[24].

Healthcare professionals should monitor ECMO patients for CRBSIs. Local erythema at cannula entry sites, purulent drainage, and positive cultures suggest the presence of CRBSIs[24,25]. However, body temperature adjustment via the ECMO system and other invasive interventions other than ECMO cannulas fall short of explaining the relationship between CRBSIs and ECMO[13,26,27]. High hemorrhagic complications during extracorporeal circulation may increase the risk of bacterial transmission from colonized sites (e.g., gut), leading to hemodynamic instability and impaired peripheral perfusion. Moreover, most infection symptoms are associated with low biocompatibility of extracorporeal circuits. This may lead to activation of the inflammatory response, leukocytosis, and ECMO circuit disruption[28].

Diagnosis

Clinical signs (e.g., fever, tachycardia, and hypotension) and lab results (e.g., C-reactive protein and procalcitonin) must be focused to diagnose CRBSIs. However, blood and catheter cultures are required for definitive diagnosis[29,30]. According to the Centers for Disease Control and Prevention, CRBSI is defined as two separate positive blood cultures for a pathogenic organism with signs of infection, including leukocytosis, leukopenia, fever, or hypothermia[31]. The most common pathogens associated with CRBSIs in ECMO are coagulase-negative staphylococci (57.9%)[3]. The most frequently reported strain types are *S. aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae, Staphylococcus epidermidis, S. aureus, E. coli, Enterobacteriaceae, Enterococcus faecium, C. albicans*, *C. parapsilosi*, and *Candida glabrata*[32-36].

Allou et al. observed bacteremia in 6 out of 10 patients (59.7%). They stated that the most frequently isolated bacteria were *Enterobacteriaceae* (38%), *Staphylococcus* spp. (28.2%), and *P. aeruginosa* (18.3%)[19]. Selçuk et al. determined that the agents in positive culture results were *Klebsiella* (8.7%), *Streptococcus* (4.8%), *Acinetobacter* (4.0%), *Enterobacter cloacae* (3.2%), coagulase-negative staphylococci (3.2%), *E. coli* (2. 4%), *Pseudomonas* (2.4%), *Serratia* (1.6%), *Citrobacter* (1.6%), *Proteus* (0.8%), *Haemophilus* (0.8%), *Listeria* (0.8%), and *Corynebacterium* (0.8%)[22].

Haneke et al. compared the results of ECMO survivors and non-survivors. They found that staphylococci (*S. aureus*, of which 22% were methicillin-resistant *S. aureus*) were the most commonly isolated bacteria in both groups. They also reported that fungi were isolated with the second-highest frequency and that most of those cases were in the non-surviving group. They detected pathogens in blood cultures, tracheal secretions, and urine. *Enterobacter* spp., *K. pneumoniae*, and *P. aeruginosa* showed a high incidence in the samples isolated from tracheal secretions[25].

Recommendations for infection control

In 2008, the ELSO issued a guideline based on ECMO-related risk factors and general principles for infection control[37]. Table 1 summarizes the strategies, staff training, surveillance practices, and preventive health measures for CRBSI prevention according to the guidelines[37]. However, there is a lack of data to guide healthcare professionals in preventing most CRBSIs and other possible complications and in the care management of ECMO patients. The data limited to the United States show variability in cannula placement and care practices performed in ECMO centers[4].

The current recommendations are only partially relevant to ECMO support. There is insufficient evidence to guide effective line fixation, dressing, and care practices to prevent decannulation and/or infection in ECMO patients. Healthcare professionals follow the guidelines to prevent intravascular catheter-related infections published by the Healthcare Infection Control Practices Advisory Committee (HICPAC) in caring for ECMO patients[31]. Within the scope of intravascular CRBSI recommendations, HICPAC guidelines include practices with a high level of evidence, such as surveillance practices, staff training, use of standard protocols and checklists, maximum aseptic technique

Table 1. Recommendations for the prevention of catheter-related bloodstream infections during extracorporeal membrane oxygenation support by the Extracorporeal Life Support Organization Infectious Disease Task Force.

1	Do not interrupt the ECMO system and avoid unnecessary interventions.
2	Needleless hubs should be used at all connections, stopcocks, and access sites in the circuit.
3	Use chlorhexidine to disinfect the parts of the ECMO system.
4	Administer only continuous infusions into the circuit to reduce the risk of transmission (e.g., heparin, vasopressors, inotropes, and narcotics).
5	To prevent cross-infection, isolate ECMO patients from other patients with multidrug-resistant organisms, heavily contaminated wounds, or severe infections.
6	Wash your hands frequently before interventions.
7	Avoid and remove unnecessary central venous catheters and invasive devices.

Table 2. Recommendations for the prevention of catheter-associated bloodstream infections in extracorporeal membrane oxygenation support.

Preparation	ECMO teams should be designated. The ECMO team must be trained in ECMO system set-up and patient management. Standard protocols/contact lists should be readily available. Antibiotics should not be used for prophylaxis because they increase antibiotic resistance.
Cannulation	Kits containing ECMO materials should be readily available. If possible, peripheral vessels should be preferred. Catheter placement should be performed under ultrasound guidance to reduce the number of mechanical complications. Maximum protective measures (e.g., mask, cap, goggles, sterile gloves, and sterile apron) should be taken. Hands should be disinfected with soap and water, alcohol-based solutions, or chlorhexidine. 5% chlorhexidine gluconate (KHG) should be used for skin antisepsis. If KHG is contraindicated, 70% alcohol solutions, isopropyl alcohol solutions, or povidone-iodine should be used. Before catheter insertion, antiseptics should be allowed to dry according to the manufacturer's recommendation. Not only the intervention site but the whole body should be covered with a sterile drape.
Post-ECMO cannulation care	Parenteral nutrition should be administered via a central venous catheter instead of administering concentrated glucose solution directly into the ECMO circuit. New vascular interventions at the site of ECMO cannulas should be avoided due to the risk of hematoma and infection. Folding of the cannula in the ECMO circuit should be prevented. Blood samples should preferably be collected from arterial catheters. Intermittent administration of drugs should be avoided. Instead, continuous infusions should be preferred. Catheter tips, needleless connectors, or injection ports should be used after wiping them with alcoholic chlorhexidine for at least 5 s. Nurse to patient ratio should be 1:1. Prophylactic antibiotics should be considered for patients with risk factors for central cannulation (immunocompromised states) or multidrug-resistant organisms.
Cannula entry site dressing	Sterile gauze or sterile, transparent, semi-permeable, or chlorhexidine dressings should be used to cover the cannulation site. If the patient is sweaty or has localized bleeding or oozing, gauze should be used until these problems are resolved. ECMO cannulas and other invasive sites should not come into contact with water. The transparent dressing should be replaced with a new one every 5–7 days (except in pediatric patients where the risk of catheter dislodgement outweighs the benefit of changing the dressing). Catheter sites should be monitored visually or by palpation when changing the dressing daily. If symptoms include tenderness at the cannula entry site and fever with no apparent source, the dressing should be removed to examine the site thoroughly.

and sterile precautions during catheterization, observation of the cannula entry site after catheterization, and dressings and collection of catheter culture after catheter removal[31]. Table 2 shows preventing CRBSIs in ECMO patients in line with the HICPAC and ELSO recommendations[11,31,32,35-39].

Glater-Welt et al. investigated standard practices for BSI prevention among national ECMO programs and reported five findings. First, most institutions use a standard approach to cannula dressings (82.9%). Second, more than half of the institutions send daily blood cultures as part of routine surveillance (34.2%). Third, healthcare professionals commonly use semi-permeable dressings to close cannulation sites (57.3%). Fourth, they use alcohol (48.2%), chlorhexidine (38.8%), and betadine (4.7%) to disinfect access ports when access to the ECMO circuit and ports is required. Fifth, more than half of healthcare professionals change cannula entry site dressings only when necessary (60.5%)[39]. Bull et al. found that cyanoacrylate tissue adhesive inhibited bacterial growth at the ECMO cannulation site. They concluded that cyanoacrylate tissue adhesive was an effective method to prevent or minimize accidental decannulation[40].

CONCLUSION

ECMO is an extracorporeal organ support in ICUs worldwide. Monitoring ECMO patients in cardiovascular surgery ICUs for CRBSIs is vital in terms of morbidity, mortality, hospitalization, and healthcare costs. Therefore, healthcare professionals should make individual and environmental adjustments, maintain aseptic conditions, and diagnose and manage signs and symptoms of infection to prevent the risk of CRBSI from the beginning to the end of ECMO support.

Researchers recommend care bundles with evidence-based practices in managing CRBSIs in ECMO patients. Cardiovascular surgeons, ICU specialists, nurses, and other healthcare professionals are responsible for implementing care bundles.

AUTHORS' CONTRIBUTIONS

HS: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **SG:** Conceptualization, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Image guidance for endoscopic sinus surgery: systematic review and meta-analysis

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INTRODUCTION

Chronic rhinosinusitis (CRS) is characterized by persistent symptomatic inflammation of the nasal and paranasal mucosa[1,2]. It affects 5–28% of the population and impacts patients' socioeconomic conditions and quality of life. Healthcare costs are higher for rhinosinusitis than for peptic ulcers, asthma, and hay fever[1-4].

The etiology of CRS involves bacterial superantigens, epithelial cell defects, biofilm formation, T-helper 1 and 2 inflammation, and tissue remodeling[5-8]. Endoscopic sinus surgery (ESS) has brought advances in the treatment of CRS[8]. Reducing inflammation and preventing remodeling of the mucosa by facilitating access to topical therapies are potential disease-modifying benefits of surgery[1]. However, it has the potential for complications due to its anatomical proximity with essential structures (skull base, orbit, internal carotid artery, and optic nerve)[9].

The risk of injuries is higher in revision surgeries due to the removal of anatomical landmarks in previous procedures[10-12]. The complication rate of ESS is 0.5%, which can be considered low risk[13,14]. However, complications can result in serious repercussions[13,15].

Intraoperative image-guided surgery (IGS) is a technology for confirming locations in anatomically challenging fields[10]. The tracking system allows for the real-time determination of the instrument's location related to anatomical landmarks[2,16], which may allow surgeons to treat more of the patient's disease. If a more complete surgery is performed, the quality of life of patients may be improved, and revision rates may be reduced[2,16].

There is a lack of scientific evidence to determine the indications and recommend the use of IGS in CRS[17]. This review aims to analyze trials that compare ESS with and without IGS.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed[18,19]. The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42020214791) and published in *BMJ Open*[20].

Inclusion criteria

The inclusion criteria were the clinical trials that compared the outcomes of patients with CRS who underwent ESS with and without IGS.

PICOT strategy

- Population/participants: Adults diagnosed with CRS.
- Intervention: ESS with image guidance.
- Comparator/control: ESS without image guidance.
- Outcomes: Complications, quality of life, operative time, and missed paranasal sinuses.
- Type of study: Clinical trials.

Patient and public involvement

There was no patient or public involvement in the study planning or application process, or during the analysis or dissemination of the results.

Search strategy

PubMed, Embase, Scopus, Web of Science, SciELO, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and ClinicalTrials.gov were searched with no limitations to date or language. All electronic databases were searched on November 22, 2022.

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Data collection and analysis

The articles retrieved were imported to EndNote Web, and duplicates were removed. Two authors independently screened the results by title, abstract, and full text to determine inclusion criteria. A third reviewer resolved the discrepancies.

Data extraction and management

Two independent authors extracted data from the included studies. The latter were inserted into a database. Meta-analysis was conducted on the outcomes that could be combined.

Risk of bias assessment

The Cochrane Risk of Bias tool was used to evaluate the random sequence generation, allocation concealment, blinding of participants, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other biases[21].

Assessment of heterogeneity

Heterogeneity was assessed using I^2 statistics, in which <25% was considered to indicate low heterogeneity, between 25 and 50% moderate heterogeneity, and >50% high heterogeneity.

Measures of the treatment effect

Operative time, as a continuous variable, was collected as means and standard error. The risk ratio was calculated for dichotomous data on complications and missed paranasal sinuses. This was performed using the Review Manager (RevMan, version 5.4) software.

Analysis

RevMan 5.4 was used to perform the statistical analysis. In the heterogeneity assessment, when I^2 was >50%, a random-effects model was used, whereas when I^2 was <50%, a fixed-effect model was applied.

All included studies were qualitatively summarized in Table 1 for comparison.

Grading quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the strength of the evidence on the systematic review results[22].

RESULTS

A total of 3,281 articles were retrieved from databases and imported to EndNote Web (576 were duplicates). Two independent authors screened the 2,705 titles, and 193 of the titles were assessed for eligibility based on abstracts. After full-text analysis, six studies were found to meet the inclusion criteria, of which five could be combined in the meta-analysis. The PRISMA flow diagram summarizes the study selection process (Figure 1). Qualitative synthesis is shown in Table 1.

Quality of life assessment

Two studies assessed the quality of life of patients, using different instruments or measures; thus, the data could not be combined into a meta-analysis.

Javer et al. compared the quality of life of patients with CRS who underwent ESS with and without the aid of IGS using a validated quality of life tool RSOM-31. The patients completed the form preoperatively and 6 months postoperatively. The IGS demonstrated a statistically significant improvement in all the 31 questions, while the ESS group demonstrated a statistically significant improvement in 13 of the 31 questions[23]. This study had an uneven sample size (80 patients in the IGS group and 15 patients in the control group). Moreover, there were differences in the characteristics between the two groups before the intervention. The control group had 30% of the included patients with stage 4 of the disease on CT scan, compared to 76% of the intervention group. The latter reflects in the scores of the preoperative RSOM-31, which showed higher scores for the IGS group before surgery compared to the ESS group.

Strauss et al. evaluated the subjective findings of 300 patients who underwent ESS, 150 with IGS and 150 without IGS, 6 months postoperatively. The preoperative Lund-Mckay score was similar between the two groups. In the IGS group, 73% (65 out of 89) of the patients referred to a general sense of well-being compared to 69% (49 out of 71) in the ESS group. Persistent complaints were reported by 16% (14 out of 89) of the IGS and 30% (21 out of 71) of the ESS group. Moreover, 96% of patients who underwent the procedure with IGS stated that they would undergo surgery again compared to 85% of patients who were operated on without IGS[24].

Complications

The number of complications that occurred in each group from the studies was combined in a meta-analysis, as shown in Figure 2. There was a trend toward a lower risk of complications with the use of IGS, although it did not reach statistical significance (risk ratio (RR): 0.53; 95% confidence interval (CI), 0.20–1.41; p=0.20)[25-27].

Operative room time

Stelter et al. found that the operations lasted for an average of 16 min longer with the aid of IGS than with conventional

Table 1. Qualitative synthesis of the included studies.

Study	Population	n	Results	Conclusion
Javer and Genoway[23]	CRS	IGS: 80 ESS: 15	A significant improvement in quality of life was observed following IGS compared with ESS in the sub-groups of nasal symptoms, ear symptoms, general symptoms, and practical problems.	The improvement in overall quality of life six months post-ESS appeared to be further enhanced when computer assistance was added to endoscopic sinus surgery.
Jiang and Liang[28]	CRS (revision surgery)	IGS: 51 ESS: 30	IGS: 83 out of 91 sphenoid sinuses were successfully opened. ESS: 35 out of 51 sphenoid sinuses were successfully opened.	IGS was a beneficial procedure for opening the sphenoid sinus, especially in revision cases.
Lorenz et al.[26]	CRS	IGS: 35 ESS: 35	IGS: Two patients had complications. ESS: Six patients had complications.	The question, whether by using IGS a higher security can be reached with a lower complication rate, cannot be answered so far.
Singh et al.[20]	CRS	IGS: 30 ESS: 30	IGS: No complications. Operating room time: 165.68 (±6.55) ESS: One complication (orbital swelling) Operating room time: 163.33 (±5.43)	The additional time taken for device setup and registration was effectively overcome by the reduced intraoperative time. Complications did not differ significantly with or without IGS.
Stelter et al.[27]	CRS	IGS: 80 ESS: 77	IGS: Two missed paranasal sinuses/three complications ESS: Five missed paranasal sinuses/three complications.	Navigation should have an assured place in training and teaching for paranasal sinus operations. Even if this new technology means extra costs, it was welcomed by all study participants (surgeons and patients).
Strauss et al.[24]	CRS	IGS: 150 ESS: 150	Incision-suture time: 10.1 min less with IGS. Preparation time: 7 min more with IGS. Successful sinusotomy: IGS: 31/31 | ESS: 9/40. Patient assessment: General feeling of well-being: 73% IGS/69% ESS; Minimal improvement, no improvement, or worsening 16% IGS/30% ESS; Would have the surgery again: 96% IGS/85% ESS.	The advantages of the examined navigation system compared to the gold standard of ESS are proven. Navigation assistance led to reduced intraoperative time, increased postoperative results, and lowered the workload of the surgeons.

CRS: chronic rhinosinusitis; IGS: image-guided surgery; ESS: endoscopic sinus surgery.

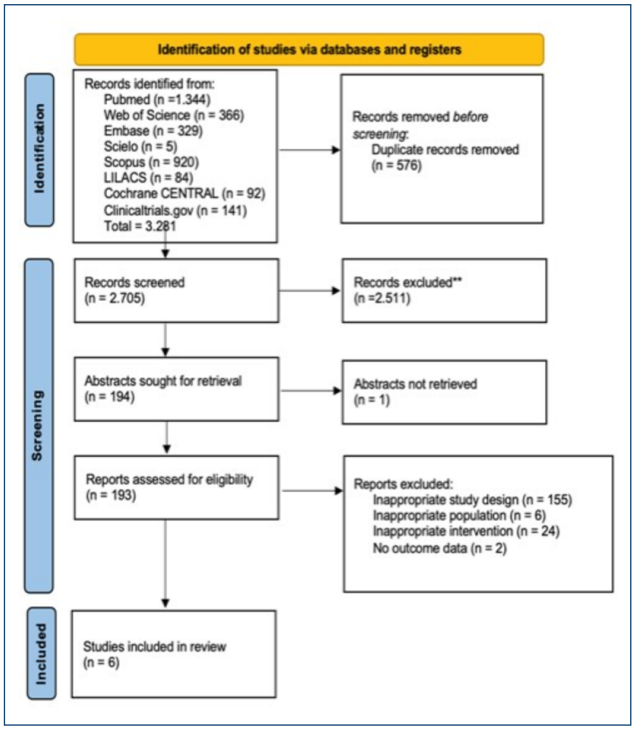

Figure 1. PRISMA flow diagram of the selection process.

ESS. Singh et al. documented a smaller difference: IGS group 165.68±6.55 (mean±SE); ESS group 163.33±5.43[25,27].

Missed paranasal sinuses

Three of the included studies evaluated the number of diseased paranasal sinuses that should have been opened during surgery but were missed. These data were combined into a meta-analysis and are presented in Figure 2. Due to high heterogeneity, a random-effects model was used to estimate the RR. A statistically significant lower incidence of missed paranasal sinuses in the IGS group was demonstrated by the RR 0.19 [0.04, 0.085], 95%CI, p=0.03[24,27,28].

Risk of bias assessment

Only Singh et al. and Stelter et al. had a clear statement regarding the randomization and allocation processes. This raises concerns about the possibility of bias in the interpretation of the review results.

The strength of the evidence assessed by GRADE was low to moderate due to the small number of events, the risk of bias in the included studies, and the high heterogeneity among the studies.

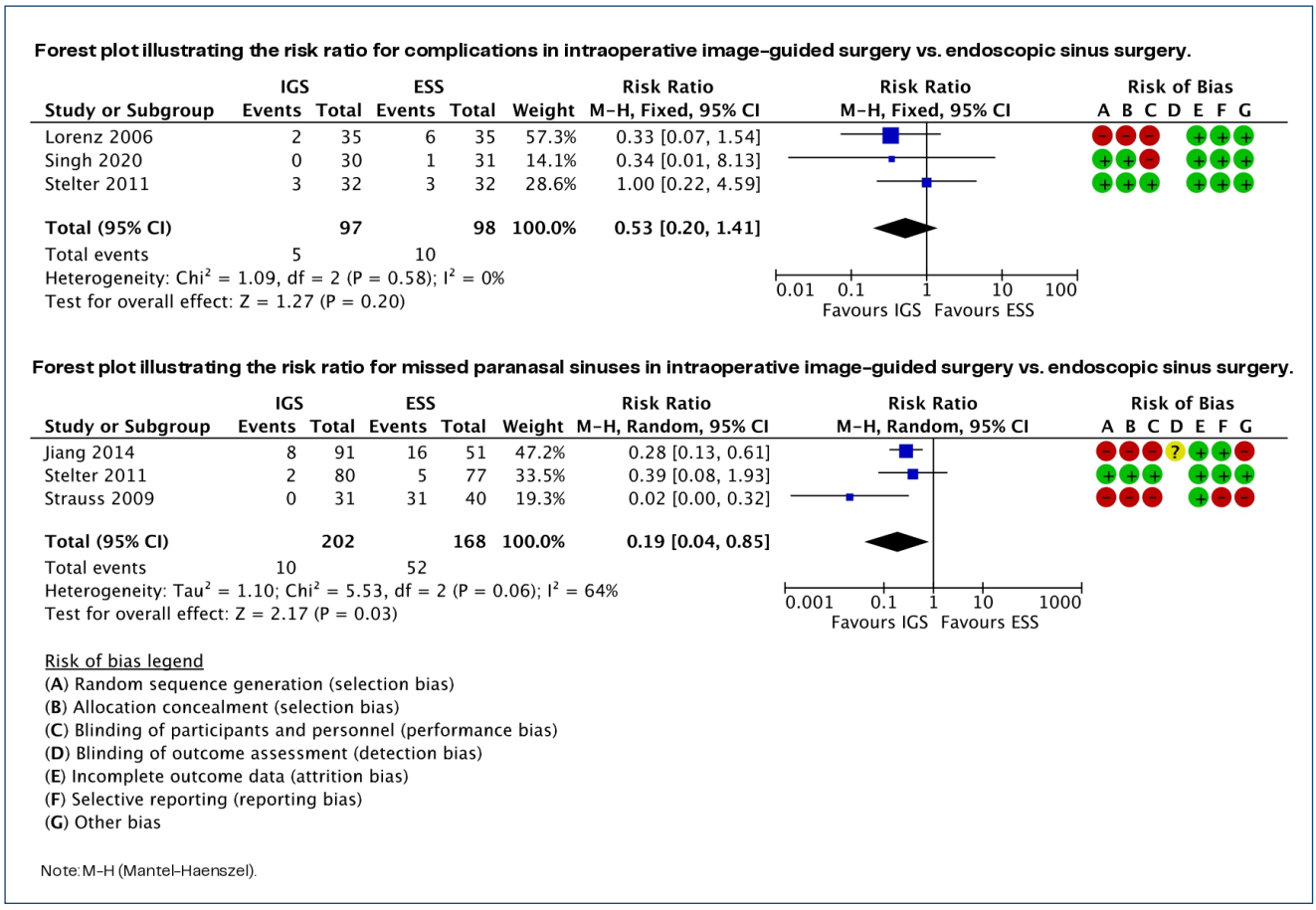

Figure 2. (A) A forest plot illustrating the risk ratio for complications in intraoperative image-guided surgery vs. endoscopic sinus surgery. (B) A forest plot illustrating the risk ratio for missed paranasal sinuses in intraoperative image-guided surgery vs. endoscopic sinus surgery.

DISCUSSION

The paranasal sinuses are anatomically close to vital and delicate structures, such as the skull base, orbit, internal carotid artery, and optic nerve. Broad and detailed anatomical knowledge is essential for surgeons to perform safe and effective procedures[8].

Intraoperative imaging provides a greater operative domain. Undoubtedly, a thorough knowledge of anatomy is essential for nasal surgeons. Nevertheless, malformations, previous surgeries, and nasal polyposis can make orientation in the surgical field difficult, even for an experienced surgeon[11].

Vreudenburg et al. and Dalgorf et al. found a reduction in the likelihood of total, major, and orbital complications in ESS with the use of IGS. They included case-control and cohort studies in their systematic reviews, while the current review did not. The small number of clinical trials on the subject was a limitation of our findings, hence the low incidence of complications in ESS[15,29].

Tschopp et al. conducted a case-control study comparing ESS with and without image guidance and did not reach statistical significance for the reduction of complications. However, they calculated the necessary sample size to achieve significant conclusions regarding the prevention of complications based on their complication rate. In their analysis, a sample size of at least 880 was necessary to draw reliable conclusions on the subject[30].

Despite the limited number of studies that conducted quality of life assessments in patients with CRS who underwent ESS with and without IGS, the evidence suggests a greater improvement in the quality of life of patients operated on with navigation. Due to the heterogeneity of the outcome measures used in the literature, it is difficult to combine or compare data from different studies[23,24].

One concern since the inception of IGS is that it would lead to an increase in operative time and therefore elevate procedure cost. Evidence from the literature suggests that IGS increases the preparation time, but it may lead to a reduction in the incision-to-suture time, thereby compensating for the overall operating room time[25,27,30,31].

In addition to the possible decrease in the complication rate for ESS, the possibility of opening more of the diseased paranasal sinuses is an important question. This review provides evidence that IGS may be more effective than conventional ESS. To the best of our knowledge, this is the first study to present this evidence. Whether this may lead to better patient-reported outcome measures should be the subject of future research[24,27,28].

The small number of high-quality studies with a low risk of bias is a limitation of this review. New clinical trials are important to better elucidate the role of image guidance in endoscopic surgery of the paranasal sinus.

CONCLUSION

Image guidance is a valuable tool in ESS for patients with CRS. It provides the surgeon with important orientation information, increasing the efficacy of ESS in opening diseased paranasal sinuses. Moreover, IGS may reduce complication rates and improve quality of life of patients. The findings of this review are limited by the bias of the primary studies included. More high-quality clinical trials are needed to confirm this evidence.

AUTHORS' CONTRIBUTIONS

MLN: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **AKG:** Conceptualization, Project administration, Supervision, Writing – review & editing. **ACAS:** Conceptualization, Data curation, Investigation, Software, Visualization, Writing – original draft. **HPB:** Data curation, Formal Analysis. **KSM:** Formal Analysis, Methodology, Validation. **JDJ:** Project administration, Supervision, Writing – review & editing. **RNC:** Validation, Writing – review & editing.

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REVIEW ARTICLE

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Chronic endometritis and assisted reproduction: a systematic review and meta-analysis

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INTRODUCTION

Chronic endometritis (CE) is defined as a localized inflammation signaled by the infiltration of bacteria in the endometrial stroma. It has adverse implications in human reproduction, including recurrent implantation failure (RIF) and recurrent miscarriage[1-3].

Chronic endometritis can be asymptomatic, and it can cause several changes in the uterus, namely, pain, bleeding, leukorrhea, and other complications. Its prevalence significantly varies and is dependent on several factors, including inflammation of the uterus and the presence of infectious bacteria in the endometrial stroma. The incidence ranges from 10% to approximately 57% according to several studies[4-10].

A brief summary of the pathophysiology of CE would include not only various bacteria that influence the entire endometrial microenvironment but also cytokine secretions that can induce leukocyte recruitment, which in turn influences the conditions (e.g., vascularity, uterine contractility, and endometrial function) for successful implantation after *in vitro* fertilization (IVF)[11,12].

Women with chronic endometritis have fertilization difficulties in assisted reproduction; therefore, treating the pathology is essential for improving the results of infertility and assisted reproduction treatments[13-15].

The objective of this study was to carry out a systematic review and meta-analysis of the literature on the subject of chronic endometritis and reproductive outcomes.

METHODS

For the systematic reviews, we used examples and guidelines by Arya et al.[16], Hennessy et al.[17], Berstock et al.[18], and Page et al.[19]. The meta-analysis was conducted in accordance with the study by Dettori et al.[20].

Search strategy

To identify the studies for inclusion in this review, we selected articles indexed in PubMed, Google Scholar, and SciELO and published from January 2012 to February 2023. First, we chose keywords from the related articles and used MeSH international data lines to find more related keywords with closer meanings, which included ("endometritis") [MeSH Terms] [All Fields] AND ("assisted reproductive technologies") [MeSH Terms] OR ("Infertility") [MeSH Terms] [All Fields]. The search was carried out in the three databases. In PubMed, we found 91 articles with titles and abstracts worth reading. From SciELO, we extracted 15 articles, and from Google Scholar, we retrieved 47 (Figure 1).

This review was conducted according to the recommendations established by Preferred Reporting Items for Systematic Reviews and Meta-Analysis Page et al.[19].

Inclusion and exclusion criteria

Studies were included if they met the following criteria: English or Spanish or Portuguese language, *in vitro* models, theme relevance, and objectives consistent with those of this study (see the flowchart in Figure 1). There were 14 articles that met the inclusion criteria (Figure 1). The eligibility steps shown in Figure 1 were independently tracked by two different authors (ECAV and JMSJ). In case of a disagreement or contradiction, a third author (MS) stepped in and repeated the search strategy.

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Five meta-analyses were conducted comparing women diagnosed with chronic endometritis (group CE) and control women (women without the presence of the disease) (group NO CE).

Statistical analysis

For descriptive statistics, the means, standard deviations, mean differences, and odds ratios with 95% of confidence interval were calculated. Meta-analysis was carried out with the Review Manager 5.4.1 software program (Cochrane Collaboration, Oxford, UK). For the values of 95%CI and "test for overall effect size," values of p≤0.05 were assumed for significant differences[20].

RESULTS

Results of meta-analyses

The live birth rates of the two study groups were significantly different (p=0.004), meaning that women with no chronic endometritis had a higher rate of live births (Figure 2). In other words, women who underwent IVF and were treated for their endometritis, thus falling into the NO CE group (without endometritis), had a higher rate of healthy live births than pregnant women with endometritis.

The clinical pregnancy rates of the two groups also differed statistically (p≤0.00001), that is, the group of women without endometritis had a higher pregnancy rate than women with inflammatory endometrium who availed themselves of assisted reproduction techniques (Figure 3). Women with chronic endometritis had a higher rate of miscarriage and were statistically significant (p=0.0002) than the control participants. Hence, women with endometritis were found to have a greater number of miscarriages than women without comorbidity. As for maternal age, there was no statistical difference between the groups (p=0.66).

All studies selected for this systematic review were at risk for bias and the details are shown in Supplementary Figure 1. It was demonstrated that close to half of the seven domains recommended for analysis by Cochrane had an unclear risk of bias, that is, the study did not mention whether the risk of bias was present or not in the work; therefore, we regarded the lack of analysis of the risk of bias as a limitation of the study[21].

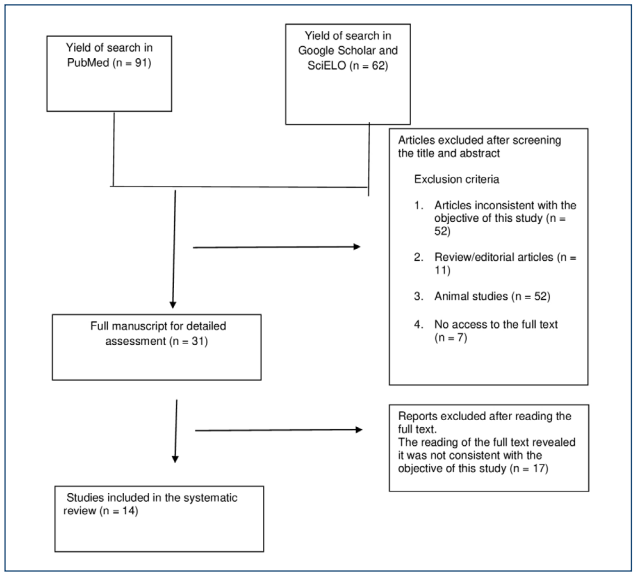

Figure 1. Flowchart of the study.

DISCUSSION

The main findings were that women without endometritis have improved rates of clinical pregnancy and live birth.

Our meta-analysis showed a significant improvement in the rates of live birth and clinical pregnancy in the group without chronic endometritis to be consistent with the literature. In the study by Cicinelli et al.[22], the live birth rate was 60% in the group treated with a CE antibiotic compared with 13% in the group that went untreated after the IVF procedures, and the clinical pregnancy rate doubled when comparing the CE and the NO CE groups[22]. Other studies that

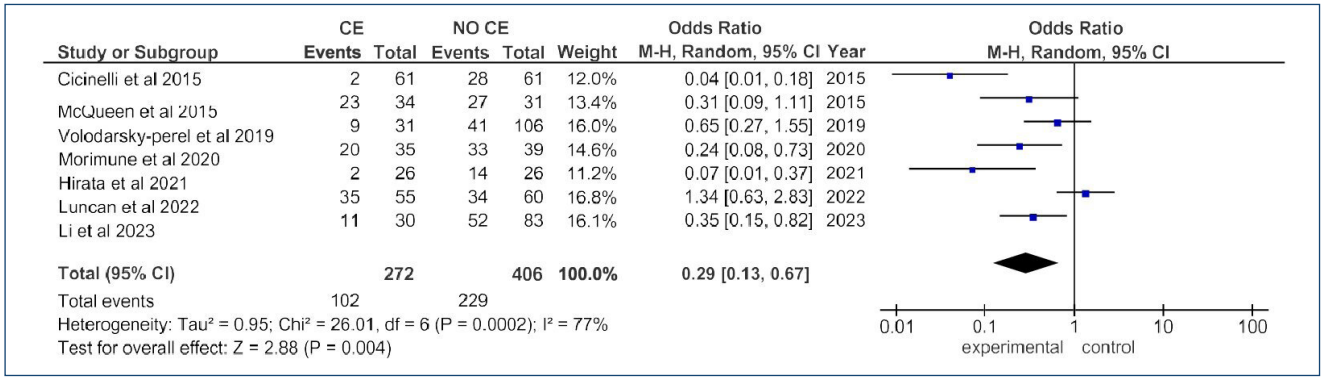

Figure 2. Comparison of the meta-analysis with the outcome live birth rate.

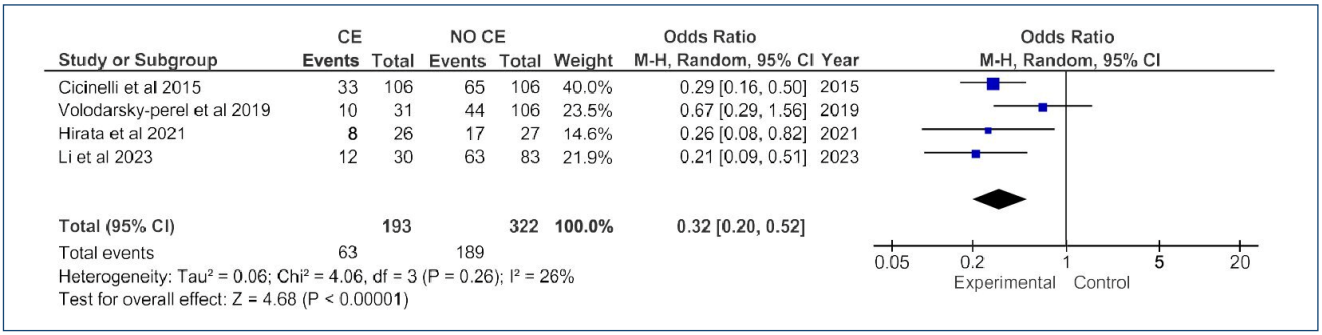

Figure 3. Meta-analyses comparing the group of women with chronic endometritis by the number of participants unit (events and total) with the group of women without chronic endometritis with respect to the clinical pregnancy rate.

corroborate our results include Yang et al.[23] and McQueen et al.[24]. More recent studies in the literature have also yielded similar results, including three meta-analyses, three analyses on women who suffered from RIF, and one study on a woman with recurrent pregnancy loss[3,25-27].

Mitter et al.[28] observed long-term recurrent pregnancy loss, including miscarriage, and found that women with chronic endometritis, whom they observed for years, were more likely to have such losses. Despite the limitations imposed by the small number of studies and events and the lack of heterogeneity, the results of our meta-analyses showed that the NO CE group had fewer miscarriages.

In short, our results are in line with the literature in that CE therapy improves clinical pregnancy rate and the course of pregnancy of patients seeking IVF. Various studies are limited by methodological problems and lack of randomization[29,30].

Strengths and limitations of the study

The strength of this study definitely lies in the positive results of the meta-analyses of the live birth and pregnancy rates. A limitation of this study is that, from the perspective of Cochrane's methodology of the seven domains of risk of bias, which we followed, the authors' analyses in most studies were incomplete, for they did not clarify whether there were any of those particular risks. In addition, the number of studies and the overall number of events and participants in the meta-analyses we performed were small.

CONCLUSION

Our study showed that women who do not have chronic endometritis have better reproductive outcomes such as better rates of live birth and clinical pregnancy.

AUTHORS' CONTRIBUTIONS

ECAV: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **JMSJ:** Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **MS:** Visualization, Writing – review & editing. **FI:** Visualization, Writing – review & editing. **LSF:** Validation, Visualization, Writing – review & editing. **AS:** Validation, Visualization, Writing – review & editing. **LAMLU:** Visualization, Writing – review & editing. **ECB:** Visualization, Writing – review & editing. **JU:** Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

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World Thyroid Day 2023 in thyroidology: no overlook thyroid dis-eases to opt for "thyroid health" purposes

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The crucial papillon gland, the thyroid, an important endocrine organ localized in front of the neck, extending laterally like an apron shield on both sides, is a delicate[1] vital organ responsible for plenty of metabolic activities, including the reproductive system and gynecologic endocrinology in *Homo sapiens* and animals, that are critical for the organisms through the secretion of thyroid hormones which makes "thyroid health" extremely important[2-10]. She (Oregon) flies with her own wings.

World Thyroid Day (WTD), *per se*, was officially accepted at an annual general meeting of the European Thyroid Association (ETA) prior to the September 2007 Congress in Leipzig, Germany, and it was formally adopted that on May 25, WTD will be celebrated in thyroidology. May 25 WTD is intended to create awareness about thyroid diseases on this special day, which was not a random pick but had a special meaning for the ETA, though the date also refers to the establishment day, founding anniversary, of ETA in 1965. Afterward, the American Thyroid Association (ATA) declared its support for this global day after WTD was first celebrated by ETA in 2010. Therefore, it is endorsed by the ATA, the sister Associations of Latin America and Asia, as well as by the International Thyroid Federation in commemoration of the butterfly-shaped delicate glands[1,11,12].

It is a day dedicated to the thyroid, augmenting awareness among both the public and authorities about the suffering of thyroid diseases all around the world. Thyroidologists are defined as the "first string" players in awareness efforts globally by the ATA in 2023[12]. Every effort is for *papillon glande thyroïde.* All roads lead to the thyroid.

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AUTHORS' CONTRIBUTIONS

DS: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **IS:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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